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Splenectomy for children and adults with persistent and chronic immune thrombocytopenia: long term results

CERTIFICATE

This is to certify that this thesis titled "Splenectomy for children and adults with persistent and chronic immune thrombocytopenia: long terms results", is a bonafide work of the candidate, Dr.Rayaz Ahmed during the period from August 2008 to August 2010 in partial fulfilment, towards the award of degree of Doctorate of Medicine (higher specialty) in Clinical Haematology for the examinations to be conducted by the Dr.M.G.R Medical University in August 2010.

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CONTENTS

ABSTRACT

Background: Although immune thrombocytopenia (ITP) is a common cause of thrombocytopenia among both children and adults, information regarding prognostic determinants of outcome of splenectomy and the management of patients who fail to respond to splenectomy is limited**.**

Aims and Objectives of the study: To analyze the response to splenectomy and to assess the response to treatment of refractory ITP post splenectomy, in children and adults with persistent and chronic ITP in our institution.

Methodology: All patients with persistent and chronic ITP seen in the Department of Haematology between 1995 and 2009 who underwent splenectomy and whose data could be retrieved were analyzed.

Results: Of the 167 adults and 87 children, 82.6% of adults and 88.5% of children were in response at 2 months post splenectomy. After a median follow up of 18.6 months *(range:1-170)* in adults and 12 months *(range: 1-173)* in children post splenectomy, 115 *(68.9%)* adults and 63 *(72.4%)* children showed a response, while 48 *(28.7%)* adults & 23 *(26.4%)* children were refractory to splenectomy. The overall mortality was 6 (3.6%) in adults and 1 (1.2%) in children. Among those who were refractory to splenectomy, subsequent drug treatment resulted in response in additional 25 (15%) of adults and 16 (17.2%) of children. The 5 & 10 year event free survival of total cases were 75.2 ± 3.7% & 71.5 ± 4.5% in adults and 79.1 ± 4.6% & 70 ± 7.5% in children respectively. Among adults, females and those who had higher platelet count at splenectomy had a higher chance of response to splenectomy. While in children, persistent phase of the disease was associated with response. The median time to post splenectomy response was shorter and the median peak platelet count was higher among those who showed sustained response in both groups.

Conclusion: In this first large series form India, comprehensively analyzing outcome of patients with ITP undergoing splenectomy, the response to treatment is similar to those reported in the literature in both adults and children from other population. Further analysis needs to be done to ascertain the predictive value of the variables associated with response.

INTRODUCTION

Immune thrombocytopenia (ITP),[12] an autoimmune disorder is a common cause of thrombocytopenia,[1] among both children and adults, characterized by the development of auto-antibodies against platelets, a spectrum of clinical severity, and a minor to severe reduction in platelet count (<100 x10^9/L). [1,12,40,54]

ITP has a combined prevalence of 1–13 per 100,000 persons[1,15], with an overall female to male ratio of 2:1[36]. Despite similar pathogenetic mechanisms, the natural history of ITP differs between children and adults. In children, the disorder is often self-limited with short course, whereas in adults it is associated with a persistent and chronic course,[12,20,34,39,48,54,55] a higher rate of complications, and an inadequate response to drug therapy[3].

Most ITP patients are treated initially with corticosteroids and, if no lasting response occurs, undergo splenectomy. [1,2,15] This initial approach results in a stable response in 60-70% of ITP patients. Even in the present era, the response rates of splenectomy are 50-85% compared to the response rates of 15-30% when steroids are administered. Since sustained responses after discontinuation of the drug occur in only 25% or less, surgical therapy is preferred as it usually gives complete response.[7]

For patients who fail to respond to splenectomy and for those who experience a loss of response after splenectomy, treatment remains difficult and undefined. However there are not many Indian data addressing these issues.[2,7] The present study is the retrospective and prospective review of the experience at our institution with splenectomy for persistent and chronic ITP in children and adults.

REVIEW OF LITERATURE:

DEFINITIONS:

Until recently, ITP was defined as isolated thrombocytopenic purpura (platelet count < 150 x10^9/L) in a patient who has no clinically apparent associated conditions or factors that can cause thrombocytopenia, including human immunodeficiency virus (HIV) infection, systemic lupus erythematosus, lymphoproliferative disorders, myelodysplasia, agammaglobulinemia, therapy with certain drugs, alloimmune thrombocytopenia, and congenital or hereditary thrombocytopenia.[1,2,30,40,65] Thrombocytopenia lasting less than 6 months was termed as acute, and greater than 6 months as chronic.[20, 30,34, 39,48,54,55]

However, an International Working Group (IWG; decided during the 5th official meeting of the European Hematology Association (EHA) Scientific Working Group on Thrombocytopenias) held on June 7, 2007, during the 12th EHA Congress in Vienna)[12] addressed the pitfalls in the definitions and terminologies used in ITP and has put forth the below mentioned recommendations (Table:1).[12]

The term "purpura" was felt inappropriate, because bleeding symptoms are absent or minimal in a large proportion of cases. The acronym ITP (now proposed to stand for **i**mmune **t**hrombocyto**p**enia) was preserved because of its widespread and time honored use and taking into account its utility for literature searches.[12]

Table:1

Proposed definitions of disease[12]	
Primary ITP	Primary ITP is an autoimmune disorder characterized by isolated thrombocytopenia (peripheral blood platelet count <100 x10^9/L) in the absence of other causes or disorders that may be associated with thrombocytopenia. The diagnosis of primary ITP remains one of exclusion; no robust clinical or laboratory parameters are currently available to establish its diagnosis with accuracy. The main clinical problem of primary ITP is an increased risk of bleeding, although bleeding symptoms may not always be present.
Secondary ITP	All forms of immune-mediated thrombocytopenia except primary ITP*
Phases of the disease	**Newly diagnosed ITP:** within 3 months from diagnosis **Persistent ITP**: between 3 to 12 months from diagnosis. Includes patients not reaching spontaneous remission or not maintaining complete response off therapy. **Chronic ITP:** lasting for more than 12 months Severe ITP: Presence of bleeding symptoms at presentation sufficient to mandate treatment, or occurrence of new bleeding symptoms requiring additional therapeutic intervention with a different platelet-enhancing agent or an increased dose

*The acronym ITP should be followed by the name of the associated disease (for thrombocytopenia after exposure to drugs, the terms "drug-induced" should be used) in parentheses: for example, "secondary ITP (lupus-associated)," "secondary ITP (HIV-associated)," and "secondary ITP (drug-induced)." For manuscript titles, abstracts, and so on, definitions such as lupus-associated ITP or HIV-associated ITP can also be used.

HISTORY:

Idiopathic thrombocytopenic purpura (ITP), also known as immune thrombocytopenic purpura and autoimmune thrombocytopenic purpura, and most recently as **i**mmune **t**hrombocy**t**openia[12] has a long history. Purpura [the Latin derivative of the Greek word porphyra (Porfura), so-called for the purple-fish, was recognized by the ancients, including Hippocrates and Galen, who described purpura associated with pestilential fevers. Down the lane, Avicenna (10th century Arab physician), Amatus Lusitanus (1580) and Lazarus de la Rivie`re ([Riverius], France,1658) described purpura in association with fever and without fever. Idiopathic thrombocytopenic purpura (ITP) was first described by P.G. Werlhof in 1735 as 'Morbus Maculosus Hemorrhagicus.[73,74] In 1951, works by Harrington, and Evans et al contributed to the understanding of the 'immune component' of ITP. In the same year, Hirsch and Damashek described the important clinical

distinctions between acute and chronic ITP. [73] Kaznelson performed the first splenectomy for ITP in 1916, and it has since then remained the treatment of choice for ITP until corticosteroids were introduced in the treatment of ITP by Wintrobe et al in 1951. [5,7,73,74]

There is a lack of consensus on standardized critical definitions, outcome criteria, and terminology in primary ITP, and has not been critically analyzed. To overcome the present heterogeneity, an International Working Group of recognized expert clinicians convened a 2-day structured meeting (the Vicenza Consensus Conference, June 7, 2007) to define standard terminology and definitions for primary ITP and its different phases and criteria for the grading of severity, and clinically meaningful outcomes and response. These consensus criteria and definitions could be used by investigational clinical trials or cohort studies.[12]

EPIDEMIOLOGY:

ITP is a relatively common acquired bleeding disorder. There is very little published epidemiological data from developing countries regarding ITP.[27,84] A retrospective analysis of 1230 patients of ITP published from the All India institute of Medical sciences, reported a median age of 19.6 years (range 0.9–80) at presentation, females: male ratio of 51.1: 48.9, acute: chronic ratio of 595: 635, mean platelet counts of 34+ 18.3x10^9/L at presentation, childhood ITP (age ≤12 yr) in 46.5% and adult ITP in 53.5%.[84]

For childhood ITP, European studies reported an incidence of 5.8 cases/100,000 children and a prevalence of 4.6/100,000[27,29,36,40]. The reported prevalence in North America is slightly higher, at 7.2/100,000 children aged 1 to 14 years. In adults, the annual incidence is around 1.6/100,000, higher in middle

age when a female preponderance is observed in contrast to the equal sex distribution amongst cases of childhood ITP (prevalence rate ratio of 1.9 for female to male) and in the elderly. [29,36,40] A population based estimate of the incidence and survival of ITP in the UK reported that overall average incidence was statistically significantly higher in women (4.4, 95% CI: 4.1–4.7) compared to men (3.4; 95% CI: 3.1–3.7). [40] Among men, incidence was bimodal with peaks among ages under 18 and between 75–84 years. [40] A Danish group reported an annual incidence of adult ITP as 3.2 cases per 100,000 per year, with a median age of 56.4 years. In 2003, Neylon et al reported a median age at diagnosis of 56 years and noted an increased incidence in the > 60 year age group.[21]

ETIOLOGY AND PATHOGENESIS:

The precise mechanism underlying ITP remains largely unknown. Immune dysregulation and the development of auto-antibodies appear to play a major role. Auto-antibodies have been shown to cause accelerated platelet clearance.[22]

In vivo plasma infusion studies by Harrington et al & Shulman et al first demonstrated that a plasma factor found in most patients who had ITP resulted in thrombocytopenia in normal individuals. [29] Subsequent plasma infusion studies by Shulman et al showed that the plasma factor destroyed both autologous and homologous platelets and that the thrombocytopenia effect was dose dependent and less pronounced in splenectomised recipients, those pretreated with corticosteroids, or after reticulo-endothelial blockade induced red cell membrane.[49]

These auto-antibodies are mainly IgG, and occasionally IgM and IgA. They are present in about 50–70% of ITP patients and they recognize one or more platelet surface glycoproteins (GP) including GPIIb- IIIa, GPIb-IX and GPIa-IIa. Antibody-coated platelets are cleared via Fcγ receptors of macrophages in the reticuloendothelial system, particularly in the spleen. The auto antibodies are light-

chain restricted with an over-representation of V_{H3-30} heavy chains. They are generated through the expansion of B cell clones under the control of T helper cells and the cytokines they produce. Th1 cytokines, IL-2 and IFN-γ are increased with reduced Th2 cytokines, IL-4 and IL-5, suggesting a type-1 cytokine polarization. The antigens that initiate the autoimmune response are altered platelet proteins or even viral or bacterial products that mimic these platelet peptides; [22] as suggested by in vitro studies that the CD4+HLA-DR restricted T cells of ITP proliferate when stimulated by GPIIb-IIIa tryptic peptides or recombinant fragments but not by intact GPIIb-IIIa polypeptide. [22 ,49] Mc Millan et al showed suppression of megakaryocyte production in vitro by ITP plasma containing anti- GPIb-IX or anti-GPIIb- IIIa antibodies.[79]

Besides antibody-mediated platelet destruction, cytotoxic Tcell-mediated lysis of autologous platelets has recently been demonstrated in vitro using CD3+/CD8+ lymphocytes of patients with active ITP. T cells interact intricately with B cells to cause antibody- and/or cell-mediated platelet destruction.[22]

Studies by several groups of investigators using indium-111 (^{111}In)-labeled autologous platelets showed considerable heterogeneity in platelet turnover in chronic ITP. Although the platelet life span is often markedly decreased, in some patients the lifespan is only mildly reduced. Overall, approximately 40% of patients with ITP had a reduced platelet turnover.[39] Increased apoptosis and para-apoptosis in ITP patients' bone marrow megakaryocytes were demonstrated by ultrastructural studies done by Houwerzijl E et al, and these changes were presumed to be caused by platelet autoantibodies in vivo (inhibiting megakaryopoiesis and pro-platelet formation). [22]

So far all the studies on ITP suggest immune system dysregulation as the primary abnormality. The exact mechanism of the immune dysfunction, however,

is generally not known. It is likely that genetic and environmental factors also have a role.

Genetic factors: There is a weak association with HLAB8DR3 in patients with ITP (Stanworth et al, 2002); linked to the development or clinical course of ITP in genetically homogeneous populations, such as the Japanese (Nomura et al, 1998). Nonetheless, immune recognition as a result of HLA may be critical in development of autoimmunity in heterogeneous populations as well. [24]

Environmental factors:

Virus-associated ITP: Childhood ITP often occurs following a viral illness; probably initiates ITP either via molecular mimicry or B-cell stimulation. ITP is often associated with HIV (Bettaieb et al, 1992), Hepatitis C virus (HCV) infection (Pockros et al, 2002; Zhang et al, 2003) and EBV infection. [24]

MMR vaccine: Severe thrombocytopenia has been observed in children, in their second year of life following MMR vaccination. The exact pathogenesis is unclear.[24]

Bacteria-associated ITP: H. pylori: There is strong evidence for an association between infection with H. pylori and ITP; related to molecular mimicry. H. Pylori strains shows geographic variations in the cytotoxin-associated gene A (CagA), which seems to correlate with the geographic variations in the incidence of H. Pylori associated ITP. [24]

CLINICAL FEATURES:

The signs and symptoms of ITP may be generalized into two categories: dry and wet purpura. Dry purpura (cutaneous haemorrhage) appears as bruising or petechiae. In contrast, wet purpura is associated with bleeding of the mucous membranes including those of the gastrointestinal tract, mouth, nose and eyes. ITP in children is usually an acute self-limiting disease, characterized by the sudden

onset of petechiae or purpura approximately 2–3 weeks after viral infection or immunization. Boys and girls are affected equally and the peak of onset is normally around 5 yrs of age. In over 70% of cases, it resolves within 6 months.

On the other hand, ITP in adults is usually persistent and chronic[12] and has a subtle onset, with no prodromal illness. Some patients with ITP are asymptomatic or have only mild bruising while others with platelet counts below 30 $x10^9/L$ are thought to be at a high risk of serious bleeding events. Indeed, the most frequent cause of death in association with ITP is intracranial bleeding, with an estimated 5% rate of fatal haemorrhage in adults.[22,26]

Physical examination usually reveals no abnormal signs, and specifically no splenomegaly. A study from the All India Institute of Medical Sciences, New Delhi, reported the incidence of presenting features as follows: skin bleed – 91.1%; mucosal bleed – 57.5%; hematuria – 7.2%; gastrointestinal bleed – 12.5% , intracraniall bleed – 2.8% and per-vaginal bleeding – 31.2 % of females. History of preceding viral fever was seen in 13.1% and palpable spleen in 2.5%.[84]

Table: 2 **Diagnostic criteria for ITP**[27]

History
Bleeding symptoms (type, severity, and duration of bleeding)
Systemic symptoms (weight loss, fever, headache, and symptoms of autoimmune disorders)
Risk factors for HIV infection
Pregnancy status
Medication (heparin, alcohol, quinine, sulphonamides, aspirin)
Family history
Physical examination
Bleeding signs
Liver, spleen, lymph nodes, and jaundice
Evidence of infection, autoimmune disease, and thrombosis
Isolated thrombocytopenia (low platelet count with an otherwise normal complete blood count and blood smear)
Exclusion of pseudothrombocytopenia (EDTA artefact)
Absence of
Other autoimmune diseases
Disseminated intravascular coagulation
Drug-induced thrombocytopenia
HIV infection
Lymphoproliferative disorders
Myelodysplasia
Agammaglobulinaemia
Allo immune, congenital or hereditary thrombocytopenia

Clinical history and physical examination (Table:2) should be directed specifically to exclude thrombocytopenia secondary to diseases such as systemic lupus erythematosus, antiphospholipid syndrome, immunodeficiency states, lymphoproliferative disorders, infection with human immunodeficiency virus, hepatitis C and H. pylori, as well as acquired thrombocytopenic disorders (e.g., bone marrow disorders and liver disease).

DIAGNOSIS:

ITP remains a diagnosis made after exclusion of other causes of thrombocytopenia. Laboratory studies (Table 3, & 4) and history are the mainstay of diagnosis.[20] It is usually not necessary to perform a bone marrow aspirate with isolated thrombocytopenia if a thorough physical examination and review of the blood smear is performed. However, bone marrow examination is recommended in the following situations; more than one cell lineage is decreased and the patient has splenomegaly or adenopathy, patients scheduled for splenectomy, adults with atypical features at diagnosis or in those >60 years, and prior to administration of medications such as steroids, which might confound the diagnosis of leukemia, delay therapy, or trigger an unrecognized tumor lysis syndrome. [20,21,22,27,70]

Antiplatelet autoantibody testing has flourished over the past 20 years, but it is rarely used to make the diagnosis of acute ITP in children as the other forms of thrombocytopenia, can generally be readily distinguished without this assay. Assays used to identify target antigens on the platelet surface have been used to in clinical research along with measurement of platelet bound autoantibody isotype using flow cytometry to determine whether certain antibodies are more likely to predict a more severe or chronic form of ITP. [20] Although there are techniques available to measure antibodies with glycoprotein IIb/IIIa and Ib/IX, IV and V

specificity, both platelet-associated and free in the plasma, the lack of sufficient sensitivity makes them of little diagnostic value. [20,22]

Table:3 **Common laboratory tests in thrombocytopenic patient at presentation.**[20]

Complete blood count and differential review smear	Rule out: Multilineage involvement leukemia or aplastic/myelodysplasia Evaluate platelet size (giant or "dust-like")
Reticulocyte count	Hemolytic anemia or chronic blood loss
Blood type, Rh, antibody screen	Possible anti-D antibody treatment Autoimmune hemolytic disease
Chemistry panel	Eliminate systemic disease, i.e., hemolytic uremic syndrome, hepatitis, hemolysis, occult malignancy with elevated LDH or uric acid
DIC screen	Sepsis, Kasabach-Merritt syndrome
Quantitative immunoglobulin levels	Rule out: common variable immune deficiency, Wiscott-Aldrich syndrome
Viral titers/PCR	Cytomegalovirus, Epstein-Barr virus, Human immundeficiency virus
Collagen vascular panel (ANA, anti-DNA)	Older patients, especially those with more chronic onset

Table:4 **Specialized laboratory tests evaluated as ITP diagnostic tools**[26]

• The direct platelet immunofluorescence test (PIFT) may be used to detect the presence of platelet-associated utoantibodies, particularly in patients with bone marrow failure and immune-mediated thrombocytopenia, and drug-dependent immune thrombocytopenia. PIFT may also be used to monitor the effect of third-line treatment in ITP patients refractory to first- and second-line treatments
• A thrombopoietin (TPO) assay may be useful in distinguishing between reduced platelet production (high TPO level) and increased platelet destruction (normal-to-low TPO level) as a cause of low platelet levels (33); however, this test is not readily available and its routine use is not justified in the diagnosis of adult patient
• Measurement of platelet RNA by flow cytometry can be used to assess platelet maturity; reticulated platelets increase with platelet production (28, 34), but again this test is not considered to be of great benefit in ITP patients
• Serological assays and breath tests can be used to detect for the Helicobacter pylori microorganism that has been reported in someITP patients (28). Eradication of H. pylori may result in an increased platelet number and it is worthwhile testing for it, especially in countries of high background incidence
• Fluorescent antinuclear antibody testing can be used to indicate chronicity in adult and childhood ITP (35); however, its routine use in the diagnosis of ITP patients is not considered beneficial

TREATMENT:

Principles of management:

Hemostatic platelet count: The primary aim of treatment of patients with ITP is to maintain a hemostatic but 'not' necessarily a normal platelet count. The risk of bleeding is minimal when the platelet count is above 30 $x10^9$/L; below that level

the bleeding risk increases progressively, and it is highest <10 x10^9/L. Major bleeding including intracranial hemorrhage usually occurs when the platelet count is <20 x10^9/L. However, the presence of other risk factors can increase the risk of bleeding such as (i) old age, (ii) platelet dysfunction, (iii) coagulation defects, (iv) anatomic defects (active peptic ulcer, recent surgery and multiple trauma), (v) uncontrolled hypertension, and (vi) infection. In the presence of these risk factors, the platelet count should be kept at a higher level, >50 x10^9/ L, or higher depending on the clinical situation.[12,22]

Emergency treatment: ITP patients with severe thrombocytopenia will require their platelet count to be raised rapidly if they have a major bleed or if they need emergency surgery. Emergency treatment includes methylprednisolone (1.0 g/ day in adults & 30 mg/kg/day in children IV for 3 days) and/or high-dose IVIG (1.0 g/kg/ day for 2 days) . Anti-D immunoglobulin (75µg/kg IV) may also be used in Rh D-positive presplenectomy individuals. Supportive treatments include; fibrinolysis inhibitors (tranexamic acid, [cyklokapron], ε-aminocaproic acid [Amicar]), direct pressure on accessible bleeding sites (e.g., nasal packing) and progestational agents (to control menorrhagia) and Recombinant factor VIIa (in uncontrolled bleeding).[22,42]

Pre-splenectomy therapy:

Initial treatment:

In patients with platelet counts <30 x10^9/ L), the aim of treatment is to obtain a stable, safe count and minimal side effects. Treatment options include corticosteroids, IVIG and anti-D.[22,42]

Corticosteroids: Prednisone is started at a dose of 1 mg/kg, and after 2–4 weeks the dose is tapered slowly to maintain a safe count with minimal side effects. A good initial response is seen in 85% and a sustained response in 50%. This

regimen has advantages in being inexpensive and avoiding side effects from prolonged steroid treatment such as osteoporosis, impaired glucose tolerance, opportunistic infections and emotional lability. [22]A single randomized trial showed no difference in response to low dose 0.25 mg/kg/d vs 1 mg/kg/d in 160 children and 223 adults (Bellucci et al, 1988). Long-term remission is seen in only 10–20% of patients following cessation of prednisolone therapy.[42]

Other steroid regimen:

High dose methyl prednisolone: A small study (Ozer et al, 2000) on 22 children given an oral 7 day course (30 mg/kg/d for 3 days followed by 20 mg/kg/day for 4 days) demonstrated that all patients achieved platelet counts > 50 x 10^9/L by day 7. Courses were repeated monthly if the count was less than 20 x10^9/L on day 30, for up to six courses.[42]

Pulsed high dose dexamethasone: Pulsed high dose dexamethasone. This treatment appears to be less effective in children than in adults in producing long-term remission, but may be useful as a temporary measure. Three small studies of 11 (Kuhne et al, 1997), 17 (Borgna-Pignatti et al, 1997) and 7 children (Chen et al, 1997) demonstrated some benefit in some children – 78% children achieved a platelet count > 100 x 10^9/L within 72 hours in 41 cycles of treatment given to 11 children with chronic ITP. [42]

IVIG: Appropriate dose of IVIG is 1 g/kg/ day for 1 day, and 2 days for severe ITP. Non-responders may benefit from another dose on day 3. IVIG only has a transient effect with median time to relapse of 11 days.[22] IVIG is generally well tolerated, the adverse reactions include headaches, fever, nausea, and increased blood pressure. Caution must be applied to patients with IgA deficiency and in particular, those with diabetes mellitus, preexisting renal disease, and old age (>70

years) in view of the reports of renal impairment with sucrose-containing preparations. [22]

Anti-D immunoglobulin: This should be given only to Rh-positive patients pre-splenectomy. IV intermittent infusions can be given at 50–75 μg/kg/day whenever the platelet count drops below 30 $x10^9$ /L.[22] Anti-D immunoglobulin can rarely cause intravascular haemolysis and disseminated intravascular coagulation. Anti-D should not be used, or used with extreme care, in patients with a positive direct antiglobulin test and a haemoglobin level that is less than 10 g/dl, due to the risk of increasing the severity of the anemia.[39]

Subsequent treatment: If the platelet count remains persistently below 30 $x10^9$ /L on low-dose steroid, danazol or azathioprine is usually added. Another alternative is to use rituximab (anti-CD20). Other options are also available; the choice of any particular treatment depends on the physician's preference. [22]

The aim of treatment is to keep the platelet count at a safe level without significant toxicity for 3–6 months until a decision on splenectomy is made or until remission is achieved.[22] According to the recent recommendation by the International Working Group, chances of spontaneous remissions are still significant during the 3-12 months period from diagnosis, making deferral of more aggressive therapeutic approaches (such as splenectomy) worthy of consideration.[12]

Splenectomy: Splenectomy removes not only the site of platelet destruction but also an organ containing autoantibody-producing B-cells. It is the single most effective therapy for chronic adult ITP with a complete durable response rate of

66% and an additional of 22% partial response.[22] Splenectomy is recommended if (i) safe platelet counts

cannot be maintained; (ii) remission is considered unlikely; (iii) drug toxicity is severe; or (iv) treatments become burdensome, e.g., frequent blood tests or loss of work time, etc. Splenectomy used to be usually recommended 3–6 months after initial diagnosis. The International Working Group (June,2007), recommends to defer splenectomy during the first 3-12 months from diagnosis as chances of spontaneous remissions are still significant during this period.[12]

However, in practice splenectomy is often delayed due to various reasons. The procedure is generally safe (mortality rates of 0.2 and 1.0% with laparoscopy and open laparotomy, respectively).[22] Laparoscopic surgery is associated with lower morbidity, speedier recovery, and shorter hospitalization. Patients with counts $<50 \times 10^9$/L may require pre-splenectomy treatment such as IVIG, anti-D, or steroids to boost the platelet count. Intra-operative platelet support may be necessary in patients who still have severe thrombocytopenia but platelets should be given after the splenic artery has been clamped.[22]

Long-term complications of splenectomy are overwhelming bacterial sepsis and thrombosis; both are rare. The incidence of fatal infection after splenectomy is approximately 0.73 per 1000 patient-years. The patient should be immunized using haemophilus influenzae type b, pneumococcal and meningococcal vaccination at least 2 weeks prior to surgery. The BCSHTF guidelines recommend life-long prophylactic phenoxy-methypenicillin or erythromycin to reduce the incidence of post-splenectomy pneumococcal infection. Revaccination with pneumococcal vaccine is required every 5 years. [22]

Post-splenectomy treatment:

(also applies to those unfit or unwilling to have splenectomy)

There is little or no evidence-based data to guide management in post-splenectomy ITP patients. One major difference between the initial treatment and post splenectomy treatment is that the latter is likely to be prolonged, and may last for months and even years. [22]A systemic review by Wesely et al showed that the post-splenectomy patients may be quite refractory to treatment; about 46% failed to respond.[3] The aim is again to attain safe platelet counts with minimal drug toxicity. Patients with platelet counts persistently below $30x10^9$/L may be treated but those with counts<$10x10^9$/L has a greater need of treatment

First-line therapy:

Patients who relapse after splenectomy usually respond to drugs used in the initial treatment such as corticosteroids and IVIG if they had responded previously. The exception is anti-D which is not effective in post-splenectomy patients. As the patients are likely to require more prolonged treatment, it is important to minimize or prevent drug toxicity, e.g., monitoring bone density in those on long-term corticosteroid. Another strategy is to use drug combinations such as prednisone and danazol (400–800 mg daily), taking advantage of its effect in reducing steroid dose. Experts now advocate the use of Rituximab (Mabthera, anti-CD20 chimeric fab) as a first-line therapy. The treatment regimen is the same as for treatment of lymphoma (IV 375 mg/ m^2 /week for 4 weeks). A response can occur as early as 4 weeks but may be delayed up to 4 months. Durable complete response rates of about 24% and partial response in another 34–43% have been reported.[22]

Dapsone: Dapsone at a dose of 75–100 mg daily orally may be given to older patients instead of long-term prednisone to avoid steroid side effects. Male patients

must be screened for G6PD deficiency. Response, if it occurs, is seen within 2 months but often does not last after cessation of treatment.[22]

Vinca alkaloid: Vincristine 1–2 mg/IV weekly for 4–6 weeks, usually results in a transient platelet increase in two-thirds of patients lasting between 1 and 3 weeks. It is often used only as an adjunctive therapy.[22]

Second-line therapy:

Azathioprime: Azathioprine is given in a dose of 2 mg⁄kg, usually up to a maximum of 150 mg⁄day; dose is adjusted to obtain a maximum effect without causing significant neutropenia. With azathioprine, the complete response rate is estimated to be ~18% and partial response rate 47–66%.[22]Azathioprine is slow-acting, and should be continued for up to 6 months before being deemed a failure. When a platelet response occurs the dose should be reduced, while maintaining a safe platelet count. [42]

Cyclophosphamide: Cyclophosphamide is an alkylating agent given at a dose of 1-2mg/kg/day. Complete response is seen in 27–39% and partial response 29–35%. Side effects include myelosuppression, hemorrhagic cystitis and in the long-term second malignancy and MDS. It should be avoided as much as possible in young patients, particularly females in the reproductive age group.[22]

Cyclosporine A: Cyclosporine A is given at 1.25–2.5 mg /kg/day in two divided doses. The dose is adjusted according to the recommended plasma drug levels. The potential serious adverse effects are renal impairment, hepatotoxicity, hypertension, and secondary malignancies. [22]

Third-line therapies:

For those who fail first- and second-line therapies, there are very few therapeutic options. Management of these patients is a dilemma. In old patients (>60 years) the morbidity and mortality are high, and in the young, their prognosis is unclear and

unpredictable. Many young healthy patients can tolerate persistently low platelet counts for several years without significant bleeding and yet they may suddenly suffer a fatal bleed during an infection or after incidental trauma. There is no evidence-based recommendation to treat or not to treat these patients. In some patients no treatment is an option. If a decision is made to treat, the options include:

1. **High-dose cyclophosphamide:** 1g/m^2 once every 4 weeks alone or in combination with other cytotoxic agents as used in the treatment of lymphoma.
2. **Mycophenolate mofetil**: 0.5–1.0 g twice daily orally may result in partial response (57–71%) within 3–4 weeks. Association with secondary lymphoproliferative disorders and acute leukemia has been reported.
3. **Combination immunosuppressive therapy** with azathioprine (100–200 mg /day), cyclosporine (100–200 mg/day), and mycophenolate (1–2 gm/day). It is well tolerated and a 46% response within 4–6 weeks has been reeported.[22]
4. **Monoclonal antibody** Campath-IH (anti-CD52) has been used in only a few patients with partial successes but is associated with significant side effects. [22]
5. **Staphylococcal-Protein A (Staph-A) immunoadsorption column**: This has less favorable results and significant toxicity (fever, chills, rash, respiratory distress, diarrhea, vasculitis, etc.). Although six treatments are recommended, most experts suggest a trial of three and then cessation of therapy if no response.[22]
6. **Campath-1H**: Lim et al (1993) treated six patients with refractory ITP (three patients had underlying CLL / non-Hodgkin's lymphoma and one

had Hodgkin's disease). A response was seen in four of five evaluable patients, and in three of these the response lasted more than 4–9 months. In most cases it took between 4 and 6 weeks for a response to occur. Side effects were significant and included rigors and fever during the infusion, and marked lymphopenia (< $0.1x10^9$/L) in all patients treated. Worsening of thrombocytopenia was noted in two patients during therapy. A more recent study of the use of Campath-1H in patients with a variety of cytopenias has shown that it was well tolerated with encouraging responses.[42]

Experimental therapy: Stem cell transplantation has been tried in a limited number of patients with refractory ITP with reasonable success. In a recent study reported by Huhn et al, 14 refractory ITP patients underwent G-CSF-mobilized hematopoietic stem cell transplant using high-dose cyclophosphamide (50 mg/kg/ day) for conditioning. Six patients had good durable responses (platelets >$100x10^9$ /L) with no ongoing treatment, and two partial responses over a maximum follow-up of 42 months. The procedure was fairly well tolerated with a few bleeding events, febrile episodes in all patients but no death. [22]

Thrombopoietic agents: Thrombopoietin (TPO) is a potent endogenous cytokine and the principal regulator of platelet production. The first generation of thrombopoietic growth factors are recombinant human thrombopoietin (rhTPO) and pegylated human recombinant megakaryocyte growth and development factor (PEG-rHuMGDF). Although clinical results showed that these agents were effective in promoting increases in platelet counts, clinical development was halted when studies demonstrated risk for autoantibody formation with cross-reactivity to endogenous TPO. A second generation of thrombopoietic growth factors, including TPO peptide and nonpeptide mimetics and TPO agonist antibodies,

utilizing different mechanisms to promote platelet production, are currently in development. The TPO peptide mimetic AMG531 and the nonpeptide mimetic eltrombopag are in advanced clinical trials and have both resulted in dose-dependent increases in platelets in healthy subjects and in significant increases in platelets in patients with chronic immune thrombocytopenic purpura (ITP). Currently available data on second-generation thrombopoietic growth factors (AMG 531,eltrombopag, AKR-501) suggest no evidence of the same risk for creating autoantibodies that will neutralize endogenous

TPO. Long-term treatment with thrombopoietic growth factors may lead to increased bone marrow reticulin or deposition of collagen.[62]

Other experimental therapies: In a recent report, three consecutive patients with chronic refractory ITP responded completely to treatment with etanercept, an inhibitor of tumor necrosis factor- α. These patients had failed 6–11 previous treatments.[22]

Others include a monoclonal antibody against Fcγ RI (MDX-33), CTLA-4 immunoglobulin or anti-CD40 ligand. The latter trial was stopped early because of thrombosis. [22]

RESPONSE TO TREATMENT:

Definition of response: The definition of a treatment response according to the current recommendation by IWG is that; it should ideally reflect clinically important endpoints including bleeding and quality of life, rather than rely exclusively on surrogate end points (platelet count) with arbitrary thresholds. Nevertheless, the platelet count is a useful measure of response that is objective, clinically relevant, and easily compared (Table:5 & 6)

Table :5 **Proposed criteria for assessing response to ITP treatments:** [12]

Quality of response*†
● **Complete response (CR)**: platelet count ≥ 100 x10^9/L and absence of bleeding
● **Response (R)**: platelet count ≥ 30 x10^9/L and at least 2-fold increase the baseline count and absence of bleeding
● **Time to response**: time from starting treatment to time of achievement of CR/R‡
● **No response (NR)**: platelet count < 30 x10^9/L or less than 2-fold increase of baseline platelet count or bleeding
● **Loss of CR or R**: platelet count below 100 x10^9/L or bleeding (from CR) or below 30 x10^9/L or less than 2-fold increase of baseline platelet count or bleeding (from R)
Timing of assessment of response to ITP treatments
● Variable, depends on the type of treatment
Duration of response§
● Measured from the achievement of CR or R to loss of CR or R
● Measured as the proportion of the cumulative time spent in CR or R during the period under examination as well as the total time observed from which the proportion is derived
Corticosteroid-dependence
● The need for ongoing or repeated doses administration of corticosteroids for at least 2 months to maintain a platelet count at or above 30x10^9/L and/or to avoid bleeding (patients with corticosteroid dependence are considered nonresponders)
Supplemental outcomes (whenever possible)
● Bleeding symptoms measured by a validated scale (requires additional studies)
● Health-related quality of life assessment measured by a validated instrument (requires additional studies)

*Platelet counts should be confirmed on at least 2 separate occasions (at least 7 days apart when used to define CR, R) or 1 day apart when used to define NR or loss of response.
†Baseline platelet count refers to platelet count at the time of starting of the investigated treatment; for post-splenectomy response evaluation, basal platelet count refers to the platelet count before patient was first treated (initial treatment). ‡Late responses not attributable to the investigated treatment should not be defined as CR or R (see Table 3). §The 2 definitions are not mutually exclusive: the first definition, collectively represented using Kaplan-Meyer analysis, is more suitable for short-course treatments aimed at inducing prolonged remission of the disease, whereas the second one is more suitable to evaluate the overall benefit of continuous or intermittent repeated administration of agents requiring dose adjustments with anticipated temporary losses of CR or R.

Table.6: **Individual agents for treatment of ITP and the time to the first and peak responses if using the reported dose range.**[12]

Agent/treatment	Reported dose range	Time to initial response*	Time to peak response*
Prednisone	1-4 mg/kg po daily x 1-4 wk	4-14 d	7-28d
Dexamethasone	40 mg po or iv daily x4 d for 4-6 courses every 14-28 d	2-14 d	4-28d
IVIg	0.4g-1 g/kg per dose iv (1-5 doses)	1-3 d	2-7d
Anti D	75µg/kg per dose iv	1-3 d	3-7 d
Rituximab	375 mg/m^2 per dose iv (4 weekly doses)	7-56 d	14-180 d
SPLENECTOMY	**LAPAROSCOPIC**	**1-56 Days**	**7-56 Days**
Vincristine	up to 2 mg/dose iv (46 weekly doses)	7-14 d	7-42 d
Vinblastine	0.1 mg/kg per dose iv (6 weekly doses)	7-14 d	7-42 d
Danazol	400800 mg po daily	14-90 d	28-180 d
Azathioprine	2 mg/kg po daily	30-90 d	30-180 d
AMG531	3-10µg/kg weekly sc	5-14 d	14-60 d
Eltrombopag	50-75 mg po daily	7-28 d	14-90 d

After splenectomy, the timing to assess the response in terms of platelet count should be within 1 to 2 months after surgery and removed from any treatment. Late responses not attributable to the investigated treatment ("spontaneous remission"), are not be defined as CR or R.[12]

REFRACTORY ITP: (Definition, therapeutic goals, and response assessment[12]

Refractory ITP (Table:7)

Definition (all should be met) ● Failure to achieve at least R or loss of R after splenectomy ● Need of treatment(s) (including, but not limited to, low dose of corticosteroids) to minimize the risk of clinically significant bleeding. Need of on-demand or adjunctive therapy alone does not qualify the patient as refractory. ● Primary ITP confirmed by excluding other supervened causes of thrombocytopenia
Definition of on-demand therapy ● Any therapy used to temporarily increase the platelet count sufficiently to safely perform invasive procedures or in case of major bleeding or trauma
Definition of adjunctive therapy ● Any non-ITP specific therapy that may decrease bleeding (eg, antifibrinolytic agents, hormonal agents, DDAVP, recombinant factor VIIa, fibrin sealants). Platelet transfusion is also included.
Definition of response to therapy in refractory ITP ● Ability to maintain a platelet count sufficient to prevent clinically significant bleeding ● Ability to decrease toxic therapy (eg, corticosteroids) does not qualify for response but should be reported
Definition of response to on-demand therapy ● Control of bleeding in the specific situation ● Achievement of a platelet count sufficient to perform procedure or minimize bleeding from trauma

The main goal of therapy in refractory ITP is generally the achievement of a platelet count sufficient to prevent clinically significant bleeding with the least toxicity. So, in this population, treatments should be evaluated for the potential to

induce an acute response and also a long-lasting response with minimum side effects/toxicity. As for any other phase of the disease, adjunctive or combination therapy or even platelet transfusion may be required for severe mucosal/organ or life-threatening bleeding.[12]

CONCLUDING REMARKS:

ITP is an autoimmune disorder in which platelets are destroyed by an antibody mediated and cytotoxic T cell-mediated process. Diagnosis is made clinically by exclusion of other causes of thrombocytopenia. Only patients with a persistently low platelet count of <30 · 109 L)1 require treatment. The initial treatment is corticosteroid, high-dose IVIG or anti-D. After 3–12 months, if it is not possible to maintain a safe platelet count with minimal drug side effects, splenectomy is recommended. This has a complete response rate of about 66%.[22] A patient who fails

splenectomy, first- and second-line therapies, is a management dilemma. The therapeutic option is no treatment, third-line treatment, or experimental therapy.

AIMS AND OBJECTIVES

1. To analyze the response to splenectomy in children and adults with persistent and chronic immune thrombocytopenia.
2. To assess response to treatment of refractory immune thrombocytopenia in children and adults.

PATIENTS AND METHODS

This study protocol was approved by our Institutional Review Board (IRB).

Duration of the Scheme: January 1995 to July 2009.

Settings of the study: Department of Clinical Hematology,

Diagnostic criteria: Immune thrombocytopenia (ITP) was diagnosed, according to the guidelines of the American Society of Hematology, as isolated thrombocytopenia (peripheral blood platelet count <100 $x10^9/L$)[12] in a patient who has no clinically apparent associated conditions or factors that can cause thrombocytopenia, including human immunodeficiency virus (HIV) infection, systemic lupus erythematosus, lymphoproliferative disorders, myelodysplasia, agammaglobulinemia, therapy with certain drugs, alloimmune thrombocytopenia, and congenital or hereditary thrombocytopenia[12] .

Splenectomy was generally performed when patients did not respond to medical therapy.

PATIENTS

Inclusion criteria:

All patients seen in the Department of Clinical Haematology between January 1995 to July 2009 with persistent or chronic immune thrombocytopenia[12], and had undergone therapeutic splenectomy were included in this study if they had a minimum follow up of 3 months.

Exclusion criteria:

- Patients with insufficient data to assess response (a minimum of 2 post splenectomy platelet counts at least one week apart).
- Patients who underwent splenectomy within 3 months from the date of diagnosis (newly diagnosed immune thrombocytopenia).

METHODS

Data collection:

After approval by the IRB, the patient data base at our institution were reviewed to identify all adults (age > 14 years) and children (age ≤ 14 years) with ITP who underwent splenectomy at our institute from January 1995 to July 2009. Prospective cases were enrolled as and when splenectomy was performed. Medical information (regarding the clinical details at diagnosis, pre-splenectomy treatment, splenectomy, post splenectomy status and follow up and other co-morbidities) and blood counts were obtained from the patients themselves or parents in case of children, or review of their hospital records (laboratory reports/ physician documentation in hospital charts/hospital discharge summaries). Repeated attempts were made to contact all patients via mail (postal/electronic) for further follow up information, including details of any subsequent treatment. Patients who did not get reviewed in the last one year, and/or who failed to respond to repeated attempts of communication through mail (postal/electronic) were categorised as '**lost to follow up'**.

Response criteria:

The definition of response criteria[12] was as follows:

- **Complete response (CR)**: Platelet count ≥ 100 $x10^9$/L and absence of bleeding.
- **Response (R)**: Platelet count ≥ 30 $x10^9$/L and at least 2-fold increase the baseline count and absence of bleeding.
- **Time to response**: Time from starting treatment (splenectomy) to time of achievement of CR or R.
- **No-Response (NR)**: Platelet count < 30 $x10^9$/L or less than 2-fold increase of baseline platelet count or bleeding. (Late responses not attributable to the

investigated treatment (splenectomyare defined as **"spontaneous remission").**

- **Loss of CR or R**: platelet count below 100 $x10^9$/L or bleeding (from CR) or below 30 $x10^9$/L or less than 2-fold increase of baseline platelet count or bleeding (from R).
- **Time to loss of Response**: Time from attaining R or CR post splenectomy to loss of R (platelet count below 30 $x10^9$/L or less than 2-fold increase of baseline platelet count or bleeding [from R]).
- **Duration of response:** Measured from the achievement of CR or R to loss of CR or R; measured as the proportion of the cumulative time spent in CR or R during the period under examination as well as the total time observed from which the proportion is derived.
- **Corticosteroid-dependence:** The need for ongoing or repeated doses administration of corticosteroids for at least 2 months to maintain a platelet count at or above $30x10^9$/L and/or to avoid bleeding (patients with corticosteroid dependence are considered non-responders.
- **Refractory ITP:** Definition (all should be met)
    - Failure to achieve at least R or loss of R after splenectomy.
    - Need of treatment(s) (including, but not limited to, low dose of corticosteroids) to minimize the risk of clinically significant bleeding.† Need of on-demand or adjunctive therapy alone does not qualify the patient as refractory.
    - Primary ITP confirmed by excluding other supervened causes of thrombocytopenia.

Data analysis:

Statistical analyses were performed with SPSS (windows 11.01 version, SPSS inc, Chicago), for all variables. Descriptive statistics was calculated for all variables. The χ^2 test/ Fishers exact test or *t*-test / Mann Whitney U test was used as appropriate to compare the differences between groups for response to therapy. Overall survival (OS) was defined as the time from initiation of treatment to death or lost follow up. Event free survival (EFS) was defined as the time from initiation of treatment till first event or lost follow up. The event can be loss of response or death. The probability of OS and EFS was estimated using Kaplan-Meier method. For all tests, a two-sided *p*-value of 0.05 or less was considered statistically significant.

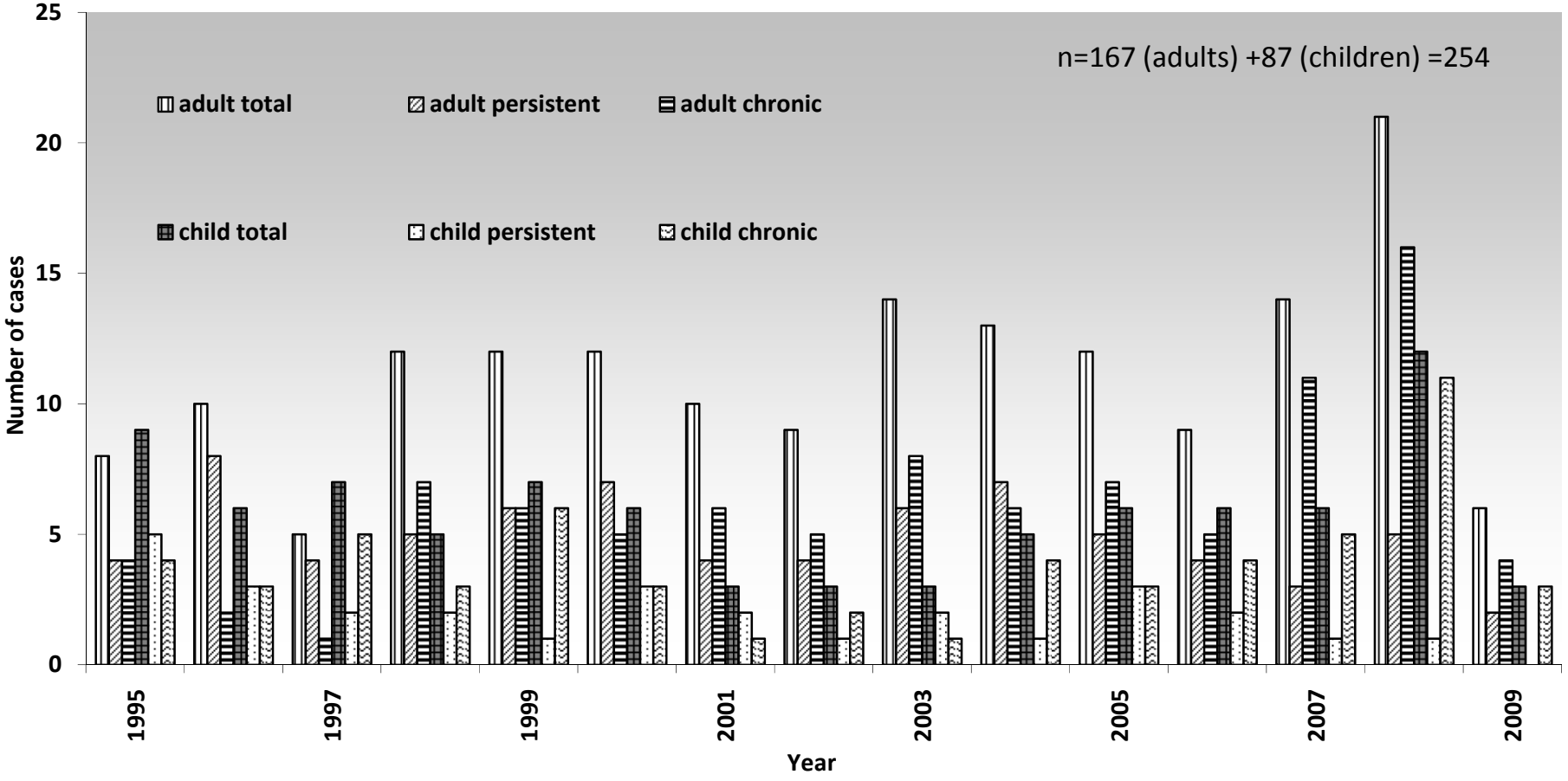
RESULTS:

Patients with ITP were categorized as adult and children ie; patients aged >14 years were considered as adults and those with age ≤ 14 years as children (age corrected to the nearest whole number). After applying afore mentioned inclusion and exclusion criteria, a total of 271 patients (173 adults and 98 children) were included in the study. This comprises 21.4% of the total splenectomies (n=1263) and 84% of the splenectomies done for ITP (n=322; including 271 cases of persistent and chronic ITP, 5 cases of newly diagnosed ITP, 6 cases of SLE, 12 cases of Evan's syndrome and 28 cases of ITP splenectomy with no details available) during the study period in this institution**.**

Of the 271 cases, for 11 children (4 male: 7 female) and 6 adults (3 male:3 female), two post splenectomy platelet values at 1 week apart couldn't be obtained from the retrievable data. These are excluded from the subsequent analysis as they do not satisfy the criteria for response/no response.

The results of the remaining 254 patients (167 adults and 87 children) are analysed below. Certain data are available on all patients while other data are available only on a portion of the patients. For each result category, the numbers of patients involved are mentioned. Adults and children are analyzed separately beneath each heading.

A. ANNUAL DISTRIBUTION OF CASES: (Fig:1)



Among the analyzed cases (n=254), the average number of splenectomy per year was 17 (11 adults and 6 children).

B. DEMOGRAPHICS OF ITP PATIENTS:

Table.1: Age and sex distribution:

Patient variables	ADULTS (n=167)	CHILDREN (n=87)
	n (%)/ Median (Range)	n (%)/ Median (Range)
Total cases		
Age at diagnosis (years)	**24** (5-64)	**8** (2-14)
Age at splenectomy (years)	**27** (16-65)	**10** (4-14)
Male :Female	**44:123**	**49:38**
Persistent ITP		
Number of cases	**74** (44.3)	**29** (33.3)
Age at diagnosis (years)	**28** (9-64)	**9** (5-14)
Age at splenectomy (years)	**28** (15-65)	**10** (6-14)
Male :Female	**16:58**	**17:12**
Chronic ITP		
Number of cases	**93** (55.7)	**58 (**66.7)
Age at diagnosis (years)	**23** (5-60)	**7** (2-13)
Age at splenectomy (years)	**27** (15-61)	**10** (4-14)
Male : Female	**28:65**	**32:26**

C. PRE-SPLENECTOMY VARIABLES:

Table.2: Clinical features at diagnosis:

Patient Variables	ADULTS (n=167)	CHILDREN (n=87)
	n (%)	n (%)
Symptoms at diagnosis		
Asymptomatic	**2** (1.2)	**1** (1.2)
Skin bleed only	**29** (17.4)	**37** (42.5)
Oro-nasal bleed only*	**5** (3)	**3** (3.4)
Skin+/oro-nasal ± other bleed#	**54** (32.3)	**40** (45.9)
Menorrhagia ± any other bleed	**69** (41.3)	**4** (4.6)
IC bleed$ ± any other bleed	**6** (3.6)	**1** (1.2)
Data not available	**2** (1.2)	**1** (1.2)
Platelet count at diagnosis **		
Median platelet count ($1x10^9$/L)	**10** (1-65)	**10** (1-41)
Patients with platelet count $\leq 10 \times 10^9$/L	**76** (56.3)	**32** (55.2)
Patients with platelet count 11-30 x 10^9/L	**49** (36.3)	**22** (37.9)
Patients with Platelet count 31-100x10^9/L	**10** (7.4)	**4** (6.9)

* Gum bleeds and epistaxis

#Gastrointstinal bleed (hematemesis, malena, hematochezia), Hematuria, subconjuctival bleed, post surgical bleed (dental extraction, TURP), $ In adults, 3 patients had intra-cerebral bleed and other 3 had subdural hematoma. In children the 1 case was with subarachnoid + vitreous bleed.

**Data for the platelet count at diagnosis was available only for 135 adults and 58 children.

Table.3: Co-morbidities at diagnosis:

Patient Variables	ADULTS (n=167)	CHILDREN (n=87)
	n (%)	n (%)
Co-morbidities		
Hypothryoidism on treatment*	**11** (6.6)	--
Hypertension/IHD/RHD^	**9** (5.4)	**1** (1.2)
Diabetes mellitus	**10** (6)	**1** (1.2)
H/o Tuberculosis/Hansen's disease#	**5** (3)	**1** (1.2)
Others$	**19** (11.4)	**6** (6.8)
Nil	**111** (66.4)	**76** (87.3)
Data not available	**2** (1.2)	**2** (2.3)

* One female patient was diagnosed to have Hashimoto's thyroiditis and another one had associated weak ANA positivity.
^ 2 adults had IHD. 1 child had history of Rheumatic heart disease (RHD)
# One adult had history of treatment for Hansen's disease and all others had history treatment for pulmonary tuberculosis..
$ Osteoarthritis, peripheral neuropathy, benign serous cystadenoma ovary, iron deficiency anemia, fistula in ano, thalassemia minor, choledochal cyst.

Table.4: Other laboratory parameters at diagnosis

Laboratory Variables		ADULTS (n=167)	CHILDREN (n=87)
		n (%)	n (%)
Auto-immune markers *			
Antinuclear antibody:	Positive	**24** (14.4)	**7** (8)
Direct coombs test:	Positive	**20** (12)	**9** (10.3)
Viral markers (n=162/83)			
Hepatitis C antibody:	Positive	--	**1** (1.2)
Hepatitis B antigen :	Positive	**2** (1.2)	--

Data for auto-immune markers was available in 109 adults and 46 children; while for viral markers data was available in 162 adults and 83 children.

* 9 adults and 2 children were tested positive for both markers (ANA & DCT).
- 3 adults and 1 child with ANA positivity were refractory to splenectomy.
- Among those positive for DCT, 5 adults and 5 children were refractory to splenectomy.
- 2 adult females with ANA positivity (1 patient positive for both ANA & DCT), developed mixed connective tissue disorder 1 year after splenectomy. The patient positive for both markers turned out to be refractory ITP but attained response to azathioprine and is in response on drug at last follow up; while the other patient, an initial responder, continues to be in response.
- One child who on follow up developed autoimmune myocarditis with left hemiparesis and transient ischemic attack (after10 years post splenectomy), was DCT positive and ANA negative at diagnosis.

Table.5: Treatment and response at diagnosis:

Patient Variables	ADULTS (n=167)	CHILDREN (n=87)
	n (%)	n (%)
Initial treatment		
Steroids*	**157** (94)	**78** (89.7)
IVIG (± Pred/M.pred)	**7** (4.2)	**9** (10.3)
Anti-D + Pred	**1** (0.6)	--
Pred+Vincristine	**1** (0.6)	--
Data not available	**1** (0.6)	--
Response to initial treatment		
Patients who responded (R+CR)	**97** (58.1)	**47** (54)
Patients in 'Response' (R)	**57** (34.1)	**24** (27.6)
Patients in 'Complete Response' (CR)	**40** (24)	**23** (26.4)
Patients in 'No Response' (NR)	**68** (40.7)	**40** (46)
Data not available	**2** (1.2)	--
Pre-splenectomy Loss of R[$]		
Patients with 1 Loss of R	**46** (66.7)	**22** (73.3)
Patients with $\geq$ 2 Loss of R	**23** (33.3)	**8** (26.7)
Median number of Loss of R	**1** (1-4)	**1** (1-3)
Subsequent treatment		
Steroids	**36** (21.6)	**23** (26.4)
Dapsone ± steroid	**32** (19.2)	**14** (16.1)
Azathioprine ± steroid	**18** (10.8)	**5** (5.7)
Dapsone + Azoran ± steroid	**42** (25.1)	**25** (28.7)
Danazol ±steroid	**4** (2.4)	--
Dapsone±Azoran + Danazol ± Steroid	**8** (4.8)	**5** (5.7)
Combination treatment[#]	**17**(10.2)	**9** (10.3)
No treatment	**8** (4.8)	**2** (2.3)
Data not available	**2** (1.2)	**4** (4.6)

*Prednisolone/Methyl Prednisolone/ Dexamethasone/ Hydrocortisone.

[$]Proper documentation of loss of Response was available only in 69 adults and 30 children.

[#]Combination of above drugs with either cyclosporine, mycophenolate, cyclophosphamide, vincristine, Anti-D or IVIG.

Table.6: Pre-splenectomy treatment response and complications:

Patient Variables	ADULTS (n=167)	CHILDREN (n=87)
	n (%)	n (%)
Overall presplenectomy response status		
Steroid dependent (SD)	**60** (36)	**26** (30)
Not responding to steroids	**27** (16.1)	**17** (19.5)
Not responding to multiple drugs[$]	**78** (46.7)	**44** (50.5)
Data not available	**2** (1.2)	--
Health problems during presplenectomy treatment period		
Steroid related problems[#]	**39** (23.3)	**8** (9.1)
Tuberculosis	**4** (2.4)	--
Dapsone related problems *	**4** (2.4)	--
Other problems[^]	**5** (3)	**1** (1.2)
No documented complications	**115** (68.9)	**78** (89.7)

[$]Dapsone, Danazol, Azathioprine, Cyclophosphamide, Mycophenolate, Cyclosporine.

[#]Hypertension. Diabetes mellitus, cushingoid features, acne vulgaris. proximal myopathy.

*Dapsone induced hemolysis, meth-hemoglobinemia, peripheral neuropathy, hepatitis.

[^]Eczema, Bell's palsy, post-infectious glomerulonephritis, epilepsy.

D. PERI-SPLENECTOMY VARIABLES^:

Table.7: Pre-splenectomy clinical status:

Patient variables	ADULTS (n=167)	CHILDREN (n=87)
	n (%)	n (%)
Clinical symptoms		
Asymptomatic	**58** (34.7)	**28** (32.2)
Skin bleed only	**14** (8.3)	**20** (23)
Oro-nasal bleed only*	**12** (7.2)	**11** (12.6)
Skin+/oro-nasal ± others #	**15** (9)	**18** (20.7)
Menorrhagia ± any other bleeds	**55** (33)	**5** (5.7)
IC bleed ± any other bleeds	**10** (6)	**3** (3.4)
Data not available	**3** (1.8)	**2** (2.4)

^The period from when the decision for splenectomy is made to immediate post splenectomy period (during hospital stay or upto 30 days, whichever is longer) * Gum bleeds and epistaxis, #Gastrointestinal bleed (hematemesis, malena, hematochezia), Hematuria, subconjuctival bleed.

Table.8: Immediate Pre-splenectomy treatment:

Treatment		ADULTS (n=167)	CHILDREN (n=87)
		n (%)	n (%)
High dose dexamethasone (HDD^)		**95** (56.9)	**41** (47.1)
Prednisolone		**18** (10.8)	**10** (11.5)
Hydrocortisone (HC^)		--	**1** (1.2)
IVIG±HDD$		**3** (1.8)	--
No treatment		**35** (20.9)	**20** (23)
Data not available		**16** (9.6)	**15** (17.2)
Platelet transfusion:	Yes	**80** (48)	**49** (56)
	No	**72** (43)	**31** (36)
	Data not available	**15** (9)	**7** (8)

^HDD=high dose dexamethasone, HC= hydrocortisone. $ 2 cases received IVIG + HDD and 1 case IVIG alone.

All emergency splenectomies except 3 adults (**1** with platelet count 175x 10^9/L, **1** with 80 x10^9/L, and one with 11 x10^9/L) and 1 child (with platelet count 9x 109/L) received PRC transfusions.

Table.9: Immediate Pre-splenectomy platelet count:

Platelet count**	**ADULT** (n=167)	**CHILDREN** (n=87)
	n (%) Median (Range)	**n (%) Median (Range)**
Median platelet count ($1x10^9$/L)	**20** (1-369)	**13** (1-182)
Platelet count $\leq 10 \times 10^9$/L	**58** (34.7%)	**32** (36.8%)
Platelet count 11-30 $x10^9$/L	**37** (22.2%)	**25** (28.7%)
Platelet count 31-100 $\times 10^9$/L	**44** (26.3%)	**16** (18.4%)
Platelet count > 100 $x10^9$/L	**24** (14.4%)	**11** (12.6%)
Data not available	**4** (2.4%)	**3** (3.5%)
Median platelet count in those who received HDD±IVIG[$] ($1x10^9$/L)	**33** (2-369)	**12** (1-182)
Median platelet count in those who received prednisolone/HC ($1x10^9$/L)	**34** (1-219)	**20** (6-180)
Median platelet count in those who received no treatment pre-splenectomy ($1x10^9$/L)	**11** (2-199)	**10** (3-146)

[$] 3 adults received IVIG along with HDD. Among those who received HDD, 53 adults (54.6%) and 13 (31.7%) children had a pre-splenectomy platelet count of >30 $x10^9$/L.

Table.10: Vaccination and surgery:

Patient variables	ADULTS (n=167)	CHILDREN (n=87)
	n (%)/ Median (Range)	**n (%) Median (Range)**
Peri-splenectomy vaccination: Patients vaccinated	**132** (79)	**64** (73.6)
Time to splenectomy from vaccination (days) [$]	**35** (0-1555)	**28** (1-1011)
Vaccination in ≤ 10 days	**27** (20.5)	**12** (18.8)
Vaccination in ≥ 11 days	**105** (79.5)	**52** (81.3)
Time to splenectomy from diagnosis (months)	**14.3** (3-290)	**18.1** (4-117)
Nature of surgery: **Elective:**		
Laparotomy	**136** (90.1)	**79** (94)
Laparoscopy	**15** (9.9)	**5** (6)
Total	**151** (90.4)	**84** (96.6)
Emergency *:	**15** (93.8)	**3** (100)
Laparotomy		
Laparoscopy	**1** (6.2)	**--**
Total	**16** (9.6)	**3** (3.4)

[$] There was no statistically significant difference in the incidence of post splenectomy sepsis among those who got vaccinated in less than or more than 10 days pre-splenectomy.

*In children, the indications were intracranial bleed in all 3 cases (1-Sub-dural hemorrhage, 1-Sub-arachnoid hemorrhage, 1-Intracerebral hemorrhage). In adults 8 were for intracranial bleed (2-SDH,1-SAH,5-Intracerebral bleed), 3 for uncontrolled gastrointestinal bleed, 1 for hemorrhage into cystadenoma ovary, and the remaining 4 were done as part of emergency surgery for other causes ie; pregnancy with fetal distess, acute calculous cholecystitis, carcinoma rectum and non-healing fistula in ano with abscess. Indication for the 1 laparoscopic emergency splenectomy was IC bleed.

Table.11: Splenectomy and immediate post splenectomy details:

Patient variables	ADULTS (n=167)	CHILDREN (n=87)
	n (%)	n (%)
Presence of splenunculi	**17** (10.2)	**16** (18.4)
Spleen HPR[$]		
Congestion	**119** (71.3)	**49** (56.3)
Follicular hyperplasia	**12** (7.2)	**15** (17.2)
Tuberculosis	**4** (2.4)	**--**
Hyaline arteriolar sclerosis	**--**	**1** (1.2)
Peri-splenectomy complications*		
Hemorrhage[@]	**9** (5.4)	**1** (1.2)
Infection[#]	**32** (19.2)	**4** (4.6)
DVT+PE	**1** (0.6)	**--**
Nil documented	**126** (75.4)	**82** (94)
Death	**4** (2.4)	**1** (1.2)
Median duration of hospital stay (days)	**9** (2-39)	**6** (3-22)
Antibiotic requirement	**78** (46.7)	**43** (49.4)

*Those occurring during hospital stay or within thirty days of surgery.

[$] Data could not be retrieved in 32 adults and 22 children. One case with splenic tuberculosis was refractory to splenectomy and the child with hyaline arteriolar sclerosis of spleen was a responder.

[@]In adults the haemorrhages were; 3 - per-operative bleed, 2 -post operative retroperitoneal bleed, 1-hematoma perineum, 1- bleed from suture site, and 1- hematuria + IC bleed.(expired), and 1- IC bleed (expired). In children, 1 case had IC bleed (expired.).

[#] the infections were; in adults, 13-had short febrile illness, 8- pneumonia, 2 - intra-abdominal collection with infection, 3 –URTI, 1-UTI , 3 -wound site infection and 2- septicemia (expired). In children, 3-had short febrile illness and 1-wound site infection. 2 adults had associated pancreatitis.

E. POST SPLENECTOMY VARIABLES:

Table.12: Initial Post splenectomy Response:

Response variables	ADULTS (n=167)	CHILDREN (n=87)
	n (%)/ Median (Range)	n (%) Median (Range)
Initial Response		
Responders (R+CR)	**148** (88.6)	**81** (93.1)
Response (R)	**21** (12.6)	**19** (21.8)
Complete Response (CR)	**127** (76)	**62** (71.3)
No Response (NR)	**15** (9)	**5** (5.7)
Expired	**4** (2.4)	**1** (1.2)
Time to initial response [days]*	**1** (1-54)	**1** (1-28)
Peak post splenectomy platelet:		
Median count [$1x10^9$/L]	**306** (1-1831)	**292** (5-2161)
Time to peak platelet count (days)	**7** (1-56)	**7** (1-50)
Initial Response with/without drug		
No drug	**140** (94.6)	**80** (98.8)
While on drug@	**8** (5.4)	**1** (1.2)
Steroid only	**3** (2)	**--**
Danazol + steroid	**1** (0.7)	**--**
Azathioprine ± steroid	**3** (2)	**1** (1.2)
Cyclosporine + steroid	**1** (0.7)	**--**
Total	**148** (88.6)	**81** (93)
Post splenectomy Loss of Response		
Patients with 1 Loss of R	**27** (82)	**15** (83.3)
Patients with ≥ 2 Loss of R	**6** (18)	**3** (16.7)
Total	**33** (22.2)	**18** (22.2)
Time to post splenectomy loss of R(months) ^	**8.8** (1-108)	**5.9** (1-116)

***The mean time to initial response in days were 5.4 for adults and 3.6 for children.**

@ The 8 adults and 1 child who responded while on treatment subsequently lost response and were eventually categorised as refractory ITP.

^In adults, 21 out of 33 (63.6%) and in children 7 out of 18 (39%) cases lost their response in the first year post splenectomy.

F. LAPAROSCOPY VERSUS LAPAROTOMY SPLENECTOMY:

Table.13: Laparoscopy versus Laparotomy*

Patient variables	Laparoscopic n (%); median (range)	Laparotomy n (%); median (range)	*p*
ADULTS: Total cases	**16** (9.6)	**151** (90.4)	
Duration of hospital stay (days)	**7.5** (3-20)	**9** (2-39)	*0.126*
Number of initial responders (R+CR)	**16** (100)	**132** (87.4)	*0.221*
Time to Initial response (days)	**3** (1-30)	**1** (1-60)	*0.378*
Post splenectomy loss of Response	**5** (31)	**28** (21.2)	*0.317*
Peri splenectomy complications	**4** (25)	**37** (24.5)	*1.000*
Late post splenectomy infection/sepsis	**4** (25)	**30** (9.8)	*0.744*
CHILDREN: Total cases	**5** (5.7)	**82** (94.3)	
Duration of hospital stay (days)	**6** (4-7)	**6** (3-22)	*0.540*
Number of initial responders (R+CR)	**5** (100)	**76** (92.7)	*1.000*
Time to Initial response (days)	**7** (1-28)	**1** (1-61)	*0.172*
Post splenectomy loss of Response	**1** (0.2)	**17** (22.4)	*1.000*
Peri splenectomy complications	--	**5** (6)	*1.000*
Late post splenectomy infection/sepsis	--	**7** (8.5)	*1.000*

*There was no statistically significant difference in any of the variables correlated

G. REFRACTORY ITP:

Refractory ITP included those cases; (1) who failed to achieve at least 'Response' (R; platelet count >30 x 10^9/L) or, after an initial response have lost Response, and (2) have severe ITP or have a risk of bleeding requiring additional treatment.

In this study all adults and children with the above characteristics are analysed as refractory cases even though the above definition is not strictly applicable to children.[12.]

The refractory cases were categorised into 5 treatment groups (detailed below; detailed description in Appendix I & II) for the purpose of analysis, depending upon the drugs they received throughout the post splenectomy treatment period.

Refractory ITP treatment groups:

Group 0 Nil (No Treatment)

Group 1 Steroid Alone

Prednisolone

Dexamethasone

Group 2 Dapsone/Azathioprine/Danazol ±Steroid:

Group 3 Combination Treatment:

Cyclophosphamide/Cyclosporine/Mycophenolate/Vincristine

with/without Group 1& 2 Drugs

Group 4 Alternative Treatment:

(Homeopathic, Siddha, Ayurvedic medicines)

Total refractory cases :

There were a total of 48 (28.7%) adults and 23 (26.4%) children who were refractory to splenectomy. In adults, the 48 refractory cases comprised of 15 patients with no response (NR) and 33 responders who eventually lost their response, and in children the 23 refractory cases included 5 with NR and 18 with loss of response respectively.

Fig:2. Refractory cases-Adults (n=48)

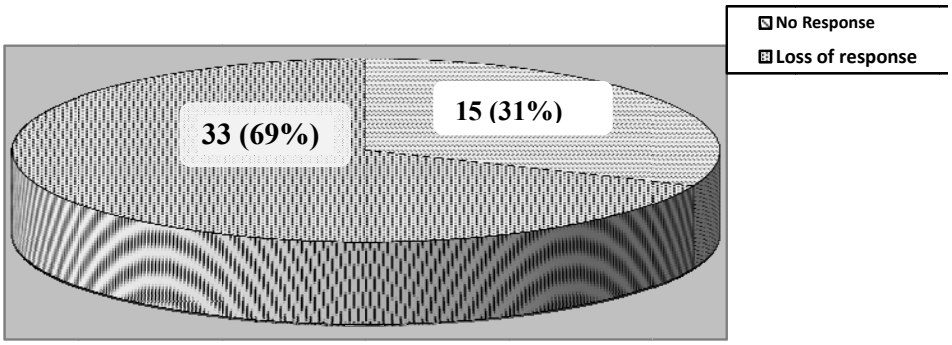
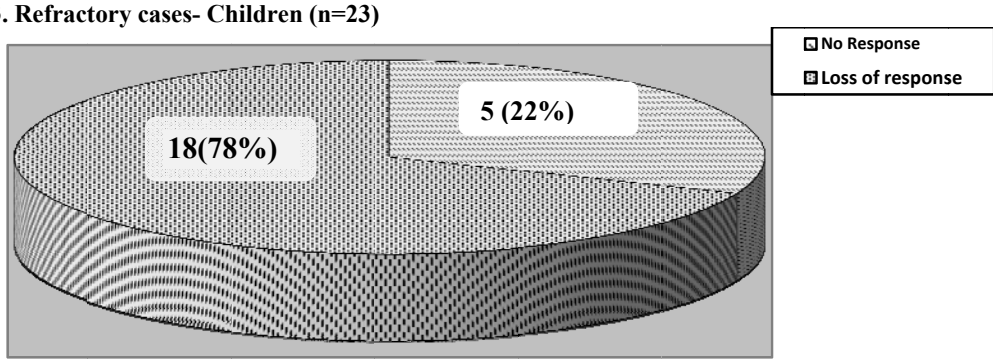


Fig:3. Refractory cases- Children (n=23)



Treatment and Response of total refractory cases:

The response to drug treatment of the total refractory cases, and the response characteristics of those patients in response at last follow up are summarised according to the treatment group they belonged to, in the tables (tables 14-17) that ensue.

Table.14: Treatment and Response of total refractory cases:

Treatment Groups*	For those who responded at any time, the duration in response (months)			Response status to treatment at last follow up		
	On drug Median(Range)	Off drug Median(Range)	Cumulative Median(Range)	In Response n (%)	Not in response n (%)	Total n (%)
	ADULTS: (n=38)			**ADULTS: (n=48)**		
Group 0	**0.5** (0-1)	**43.5** (29-58)	**44** (29-59)	**--**	**4** (17.4)	**4**(8.3)
Group 1	**1** (0-6)	**17** (1-116)	**18** (1-118)	**4** (16)	**2** (8.7)	**6**(12.5)
Group 2	**9** (0-74)	**13** (0-133)	**20** (1-145)	**16** (64)	**11** (47.8)	**27**(56.3)
Group 3	**9.5** (2-37)	**36** (7-105)	**45** (9-142)	**5** (20)	**4** (17.4)	**9**(18.8)
Group 4	--	**--**	**--**	**--**	**2** (8.7)	**2** (4.2)
Total	**3.5** (0-74)	**18** (0-133)	**22.5** (1-145)	**25** (52.1)	**23** (47.9)	**48**(100)
	CHILDREN: (n=21)			**CHILDREN: (n=23)**		
Group 0	**--**	**118**	**118**	**1** (6.3)	**1** (14.3)	**2** (8.7)
Group 1	**1** (1-2)	**18** (14-78)	**20** (15-79)	**3** (18.8)	--	**3** (13)
Group 2	**4** (0-20)	**7** (0-92)	**21** (2-101)	**10** (62.5)	**3** (42.9)	**13** (56.5)
Group 3	**1** (0-18)	**1** (0-1)	**1** (1-18)	**1** (6.3)	**3** (42.9)	**4** (17.4)
Group 4	**55**	--	**55**	**1** (6.3)	--	**1** (4.3)
Total	**3** (0-55)	**7** (0-118)	**20** (1-118)	**16** (69.6)	**7**(30.4)	**23** (100)

Treatment Groups* : see Appendix 1 & II

Table.15: Details of Refractory cases who showed response at last follow up:

Treatment Groups*	Patients in R/CR at last follow up			Time to R/CR[$] (months)	For patients who showed response at last follow up, the duration in response (months)		
	On drug n (%)	Off drug n (%)	Total n (%)	Median(Range)	On drug Median(Range)	Off drug Median(Range)	Cumulative Median(Range)
ADULTS (n=25)							
Group 0	--	--	--	--	--	--	--
Group 1	--	**4** (16)	**4** (16)	**10.1** (5-16)	**3.5** (0-6)	**25** (13-116)	**25.5** (15-118)
Group 2	**9** (36)	**7** (28)	**16** (64)	**11.2** (2-129)	**10.5** (0-36)	**19.5** (1-133)	**27** (9-145)
Group 3	**2** (8)	**3** (12)	**5** (20)	**19.4** (9-140)	**15** (3-37)	**50** (15-105)	**53** (19-142)
Group 4	--	--	--	--	--	--	--
Total	**11** (44)	**14** (56)	**25** (100)		**10** (0-37)	**24** (1-133)	**34** (9-145)
CHILDREN (n=16)							
Group 0	--	**1** (6.3)	**1** (6.3)	**12**	--	**118**	**118**
Group 1	**1** (6.3)	**2**(12.5)	**3** (18.8)	**17.7** (8-29)	**1** (1-2)	**18** (14-78)	**20** (15-79)
Group 2	**3**(18.8)	**7**(43.8)	**10** (62.5)	**10.5** (3-116)	**5** (0-20)	**30.5** (0-92)	**34.5** (2-101)
Group 3	**1** (6.3)	--	**1** (6.3)	**14.4**	**18**	--	**18**
Group 4	**1** (6.3)	--	**1** (6.3)	**78.6**	**55**	--	**55**
Total	**6** (37.5)	**10** (62.5)	**16** (100)		**4** (0-55)	**19** (0-118)	**47** (2-118)

Treatment Groups* : see Appendix 1 & II [$] Time from the date of splenectomy to the date of last response

Table.16: Treatment details of individual refractory cases who responded to treatment-Adults

Treatment Groups	Post splenectomy response		Number of cases			Follow up	Drugs to which response was noticed in the Pre-splenectomy period
	Drugs received throughout the treatment period	Drug to which responded	Total	On drug	Off drug	On /Lost (n)	
1	Pred*	Pred	2	-	2	2/-	1-Pred, Dap, Dexa (SD) 1-Pred, M.Pred*, Dan, CSA* (SD)
	Pulse Dexa	Pulse Dexa	2	-	2	1/1	2 - Pred
2	Aza*	Aza	3	1	2	2/1	1 –Dap, Pred 2-Pred
	Pred, Aza	4-Pred, Aza	4	3	1	3/1	1-Dap 2-Pred, Dap 1-Pred
	Dap*	Dapsone	5	3	2	4/1	1 -Aza 1-Pred 3-No response to any agent
	Pred, Dap	2-Pred, Dap 1-Pulse Dexa, Dap	3	2	1	3/-	1-Pulse Dexa (SD) 1-Pulse Dexa, Dap 1-No response to any agent
	Pred, Dap,Aza	Dap	1	-	1	-/1	Dap
3	Pred,Cyclo*	Pred,Cyclo	1	1	-	-/1	Pred (SD)
	Pred, CSA	Pred,CSA	1	-	1	1/-	Pred, Dap, Aza
	Pred, Dap, Aza,Cyclo	1[$]-response to all drugs 1- Pred	2	-	2	2/-	1-Pred 1- No response to any agent
	Pred,Dap,MMF*	MMF	1	1	-	1/-	Pred, Aza,Dap (SD)
Total			**25**	**11**	**14**	**19/6**	

*Pred=Prednisolone. MMF=Mycophenolate, CSA=Cyclosporine, M.Pred=Methyl prednisolone, Dexa=Dexamethasone, Aza=Azathioprine, Cyclo=Cyclophosphamide, Dap=Dapsone, Dan=Danazol. [$]1 case had total of 4 loss of responses and showed response to different combinations given following each loss of response.

60% (n=15) of adults responded to steroid based therapy. The refractory cases who responded to post splenectomy steroid treatment were found to be responsive to steroids in the pre-splenectomy period also. Those who showed response to other drugs did not show any correlation; however the numbers of cases are too small for a statistical correlation to be done.

Table.17: Treatment details of individual refractory cases who responded to treatment-Children

Treatment Groups	Post splenectomy response		Number of cases			Follow up	Drug to which response was noticed in the Pre-splenectomy period
	Drugs received throughout the treatment period	Drug to which responded	Total	On drug	Off drug	On/Lost (n)	
0	Nil	-	1	-	1	-/1	No response to any agents
1	Pulse Dexa*	Pulse Dexa	1	-	1	1/-	Pred, Dap, Aza
	Pred *	Pred	2	1	1	1/1	1- No response to any agents 1-Pred
2	Aza*	Aza	2	1	1	1/1	1- No response to any agents 1-Pred
	Dap*	Dap	2	1	1	1/1	1- No response to any agents 1-Pred
	Pred, Dap	2-Pred,Dap	2	-	2	2/-	1- No response to any agents 1-M.Pred, IVIG
	Pred,Aza	2-Pred,Aza	2	-	2	1/1	1-Pred,Dan,Dap(SD) 1-Pred, Aza,Dap(SD)
	Pred, Dap, Aza	Pred, Dap, Aza	1	1	-	-/1	No response to any agents
	Pred, Dap, Dan*	Pred, Dap, Dan	1	-	1	-/1	Pred,Dap
3	Pred, Aza,MMF*	Pred, Aza, MMF	1	1	-	1/-	Pred,Dap, Aza (SD)
4	Alternative medicine[#]	Alternative medicine[#]	1	1	-	1/-	Pred
Total			**16**	**6**	**10**	**9/7**	

*Pred=Prednisolone. MMF=Mycophenolate, CSA=Cyclosporine, M.Pred=Methyl prednisolone, Dexa=Dexamethasone, Aza=Azathioprine, Cyclo=Cyclophosphamide, Dap=Dapsone, Dan=Danazol, IVIG=IV immunoglobulin G. [#] Siddha medicine

68.7% (n=11) of children responded to steroid based therapy. The refractory cases who responded to post splenectomy steroid treatment were found to be responsive to steroids in the pre-splenectomy period also. One child who responded to Azathioprine and another who responded to Dapsone showed a similar response pattern in the pre-splenectomy period. The numbers of cases are too small for a statistical correlation to be done.

Table.18: Final response status of refractory cases versus phase of ITP

Patients	Phase of ITP at splenectomy	n	Final response to treatment		
			Responded n (%)	Not responded n(%)	*p*
Adults (n=48)	Persistent	20	10 (20.8)	10 (20.8)	*0.961*
	Chronic	28	15 (31.3)	13 (27.1)	
Children (n=23)	Persistent	3	1 (4.4)	2 (8.7)	*0.211*
	Chronic	20	15 (65.2)	5 (21.7)	

Although in children 65.2% of the refractory cases (who were in chronic phase of ITP at splenectomy) responded to treatment, the observation showed no statistical significance**.**

Table.19: Clinical status of Refractory cases at last follow up

Patient variables	ADULTS (n=48)	CHILDREN (n=23)
	n (%)	n (%)
NR + loss of R who responded to treatment	**25** (52.1)	**16** (69.6)
NR who went into spontaneous remission	--	**1** (6.2)
Patients who continued in NR:	**10** (20.8)	**2** (8.7)
Symptomatic	**3** (30)	**1** (50)
Asymptomatic	**7** (70)	**1** (50)
Expired	**1** (10)	--
On treatment	**5** (50)	**1** (50)
Patients who continued in Loss of R	**13** (27)	**5** (21.7)
Symptomatic	**6** (46)	**4** (80)
Asymptomatic	**7** (54)	**1** (20)
Expired	**1** (7.7)	--
On treatment	**9** (69)	**3** (60)
Refractory cases alive at last follow up *	**46** (95.8)	**23** (100)
Mortality	**2** (4.2)	--

***** 2 cases out of total adult 48 refractory ITP, expired while on follow up.

H. POST SPLENECTOMY MORBIDITIES AND MORTALITIES:

Table.20: Post splenectomy health problems[^]

Health variables	ADULTS (n=167)	CHILDREN (n=87)
	n (%)	n (%)
Thrombo-embolism (DVT/CAD)	**3**(1.8)	--
Intestinal obstruction	**1**(0.6)	--
Infection	**34** (20.5)	**7** (8)
Malignancy[$]	**4** (2.4)	--
Collagen vascular disease*	**2** (1.2)	**1** (1.2)
ICH	**3** (1.8)	--
Peritoneal/GI bleed	**7** (4.2)	**1** (1.2)
More than one complications	**3** (1.8)	--
Residual spleen	**1**(0.6)	--
Nil documented	**110** (65.9)	**78** (89.6)

[^] Health problems encountered anytime post splenectomy (upto the last follow –up)

[$] 1-Mantle cell lymphoma (diagnosed 2 years 8 months post splenectomy), 1-Follicular lymphoma (diagnosed 11 years 4 months post splenectomy), 1-carcinoma breast (diagnosed 10 years post splenectomy), 1-Adenocarcinoma of the stomach (diagnosed more than 1 year post splenectomy). *2 adults developed mixed connective tissue disorder (after 1 year of splenectomy) and one child developed autoimmune myocarditis with transient ischemic attack after 10 years of splenectomy.

Table.21 Mortality Details:

Patient variables	ADULTS (n=167)	CHILDREN (n=87)
	n (%)/ Median (Range)	n (%)/ Median (Range)
Sex (Male:Female)	**2:4**	**1:0**
Phase of ITP: Persistent	**3** (50)	--
Chronic	**3** (50)	**1** (100)
Time to death from splenectomy (days)	**12** (1-558)	**1**
Age at diagnosis (years)	**27.5** (16-57)	**3**
Age at splenectomy (years)	**30** (16-61)	**5**
Cause of death*:		
Bacterial sepsis	**1 (**16.7)	--
Sepsis + massive GI bleed	**1 (**16.7)	--
Sepsis + IC Bleed	**1 (**16.7)	--
Intracranial hemorrhage	**3** (50)	**1** (100)
Total	**6** (3.6)	1 (1.2)

*5 expired (4 adults and 1 child) in the early post splenectomy period. The remaining 2 adult cases expired at 16 and 19 months post splenectomy following severe gram negative sepsis + massive GI bleed, and intracerebral hemorrhage respectively. The lady who expired at 16 months post splenectomy, was an initial responder who subsequently lost response 4 months later and remained refractory to treatment (Treatment Group 3; steroid, dapsone, danazol, cyclosporine, IVIG). The second case was in "No response" (NR) throughout and remained refractory to steroid, danazol and mycophenolate (Treatment Group 3).

I. SURVIVAL CHARACTERISTICS:

Table.22: Survival characteristics:

Survival variables Data available (n=adult/children)	**ADULTS (n=167)** **n (%)** **Mean; Median (Range)**	**CHILDREN (n=87)** **n (%)** **Mean; Median (Range)**
Alive as on last follow up	**161** (96.4%)	**86** (98.8%)
Total death	**06** (3.6%)	**01** (1.2%)
Total cases on follow up^	**75** (46.6%)	**37** (43%)
Total cases lost to follow up*	**86** (53.4%)	**49** (57%)
Follow up duration (in months)		
Total cases	**38.9; 18.6** (1-170)	**33.8; 12**(1-173)
Responders (n=115/63)	**33.5; 11.9** (1-164)	**29.5; 4.5** (1-173)
Refractory cases (n=48/23)	**38.6; 38.7** (1-170)	**48.3; 20.1** (7-154)
Refractory in response (n=25/26)	**56.5; 38.4** (4-148)	**51; 20.5** (10-154)
Refractory not in response (n=23/7)	**53.8; 38.9** (1-170)	**42; 12.6** (7-125)
Overall survival[#] of:		
Total cases	93.4% ± 3% (4-290 months)	98% ± 1.6% (4-214 months)
Responders (n=115/63)	100%	100%
Refractory cases (n=48/23)	94.7% ± 3.7%	100%
Event free survival[@] of:		
Total cases (n=167/87)	71.5% ± 4.5% (0-290 months)	70% ± 7.5% (0-193 months)
At 5 yrs: Overall Survival	96.9% ± 1.6%	98% ± 1.6%
Event Free Survival	75.2 % ± 3.7%	79.1% ± 4.6%
At 10 yrs: Overall Survival	93.4% ± 3%	98% ± 1.6%
Event Free Survival	71.5 % ± 4.5%	70% ± 7.5%

^57 adults and 21 children had more than 5 years of follow up.
*52 (31%) adults and 29 (33.3%) children were lost to follow up within one year, and 72 (43%) adults and 44 (50.5%) children were lost within 5 years post splenectomy.
[#] Figure: 4 [@] Figure:5,6

Fig:4 Overall Survival: Adult total cases (n=167)

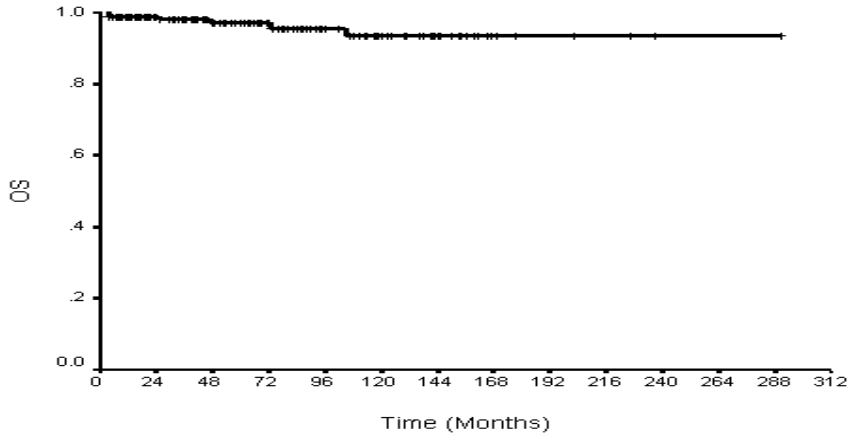


Fig:5 Event Free Survival: Adult total cases (n=167)

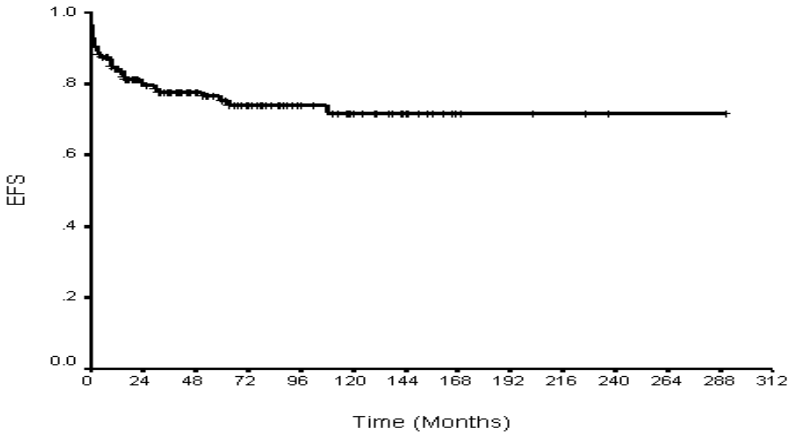
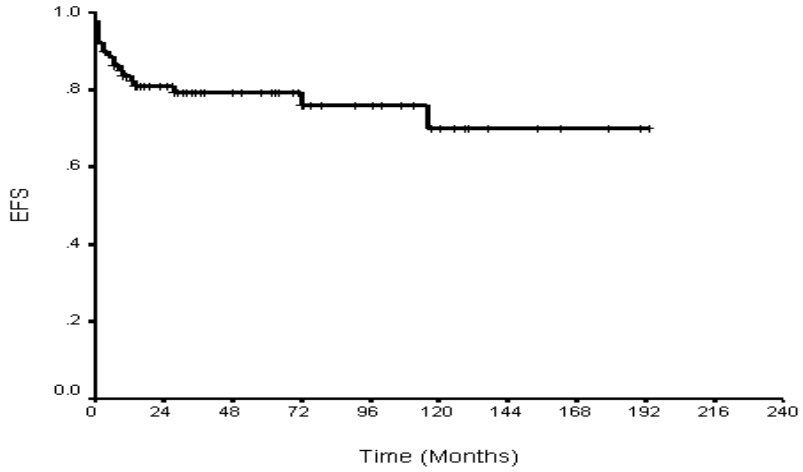


Fig:6. Event Free Survival: Child total cases (n=87)



J. Table 23. PROGNOSTIC DETERMINANTS OF RESPONSE TO SPLENECTOMY:

Variables (adult/child)	Adults (n=163) [@]			Children (n=86)[@]		
	Responders	**Refractory**	***p value***	**Responders**	**Refractory**	***p value***
Number of patients	115 (70.6%)[@]	48 (29.4)		63 (73.3%)[@]	23 (26.7)	
Presplenectomy variables:						
Male:Female	23:92	19:29	***0.011***	34:29	14:09	*0.63*
Age at diagnosis (years)	24 (5-64)	28 (12-60)	***0.061***	08 (2-14)	07 (2-14)	*0.462*
Persistent: chronic	52:63	20:28	*0.731*	26:37	03:20	***0.019***
Platelet at diagnosis ($1x10^9$/L)[$]	10 (1-65)	10 (1-49)	*0.882*	9.5 (1-40)	10 (1-41)	*0.371*
Age at splenectomy (years)[$]	26 (15-65)	31 (15-61)	***0.061***	10 (4-14)	09 (4-14)	*0.411*
Initial treatment (steroids:steroid+others) **	108:06	46:02	*0.821*	58:05	20:03	*0.433*
Response to initial treatment (R+CR:NR)**	66:47	28:20	*0.723*	35:28	12:11	*0.921*
No. of Presplenectomy loss of R (1:2)	29:16	16:5	*0.521*	16:4	6:4	*0.381*
Presplenectomy status(SD:SNR:MDNR) **	46:20:47	12:6:30	*0.071*	18:13:32	8:4:11	*0.842*
Time to splenectomy from diagnosis(mths)[$]	13.9 (3-290)	15.5 (6-167)	*0.757*	15.2 (4-117)	27 (7-69)	*0.087*
Platelet at splenectomy($1x10^9$/L)[$]	30 (2-369)	10 (2-258)	**0.004**	15.5 (1-179)	9.3 (2-182)	*0.161*
Post splenectomy variables						
Laparotomy:Laparoscopy	104:11	43:5	*1.000*	59:4	22:1	*1.000*
Splenunculi	10	07	*0.211*	14	02	*0.323*
Time to initial response (R/CR)[$] days	1 (1-55)	3 (1-60)	***0.031***	1 (1-28)	3 (1-61)	*0.138*
Peak post splenectomy platelet ($1x10^9$/L)[$]	400 (30-1831)	125 (1-1406)	***0.000***	335 (45-2161)	139 (5-1738)	***0.001***
Time to peak platelet (days)[$]	7 (1-56)	7 (1-54)	*0.152*	7 (1-50)	7 (1-50)	*0.755*

[@]Patients who expired in the immediate post splenectomy period (4 adults & 1 child) are excluded. So, n=163 in adults and n=86 in children . [#:] n (%);
[$:] median (range) **Data not available for all the 115 responders. SD:steroid dependent, SNR:steroid non- responsive, MDNR: multiple drug non responsive.

Analysis in adults showed that higher platelet count at splenectomy (***p=0.004***), female sex (***p=0.011***), shorter time to response to splenectomy ***(p=0.031)*** and higher peak post splenectomy platelet count ***(p=0.000)*** as significant predictors of response. Among responders in children, higher peak post splenectomy platelet count ***(p=0.001)*** and persistent phase of the disease ***(p=0.019)***showed a significant *p value* **.**

K. OVERALL OUTCOME: The overall post splenectomy outcome of the total cases is summarised in the table below as, '**initial response'** (ie; response at any time within the first 2 months [56 days] post splenectomy), '**response status at 2 months'** and '**at last follow up'**.

Table.24: Overall Post splenectomy outcome of total cases:

Response variables Data available (adult/children)		**Adults (n=167)**			**Children (n=87)**		
		Initial response#	**Status at 2 months#**	**At Last follow up**	**Initial response#**	**Status at 2 months#**	**At Last follow up**
		n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Initial Responders: (continued in R/CR)		**148*** (88.6)	**138$** (82.6)	**115** (68.9)	**81*** (93.1)	**77$** (88.5)	**63** (72.4)
In Response (R)		21 (12.6)	21 (12.6)	14 (8.4)	19 (21.8)	21 (24)	17 (19.5)
In Complete Response (CR)		127 (76)	117 (70.1)	101 (60.5)	62 (71.3)	56 (64.4)	46 (52.9)
Responders on follow up		--	101 (73.2)	44 (38.2)	--	53 (68.8)	25 (39.7)
Responders lost to follow up		--	37 (26.8)	71 (61.7)	--	24 (31.2)	38 (60.3)
Refractory ITP: (NR+Loss of R)		**15** (9.0)	**25** (15)	**48** (28.7)	**5** (5.7)	**9** (10.3)	**23** (26.4)
Continued in NR		15 (9.0)	15 (9.0)	10 (6)	5 (5.7)	5 (5.7)	2 (2.3)
In loss of R		--	9 (5.4)	13 (7.8)	--	3 (3.4)	5 (5.7)
Refractory cases who responded to treatment		--	1 (0.6)	25 (15)	--	1 (1.2)	15 (17.2)
NR who went into spontaneous remission		--	--	--	--	--	1 (4.3)
Refractory cases on follow up		--	23 (92)	31 (64.6)	--	9 (100)	12 (52.2)
Refractory cases lost to follow up		--	2 (8.0)	15 (31.2)	--	--	11 (47.8)
Death:	Additional deaths	**--**	--	**2**(4.2)	**--**	--	**--**
	Total death	**4** (2.4)	**4** (2.4)	**6**(3.6)	**1** (1.2)	1(1.2)	**1** (1.2)

#Time period for initial response is the first 2 months (day 1-day 56) post splenectomy. A few of those who responded initially (within day 1 –day 56) had lost their Response by the end of 2 months post splenectomy.

* Among the148 adults and 81 children who responded initially, 8 adults and 1 child achieved response while on drug treatment.

$At 2 months, out of the 148 adults and 77 children in response, 7 adults and 1 child were on drug treatment.

DISCUSSION:

Of the total 254 patients analysed, 167 were adults (age: > 14 years) and 87 were children (age: ≤ 14 years). Patients were followed up post splenectomy for a median of 18.6 months *(range:1-170; mean-38.9)* in adults and 12 months *(range: 1-173; mean-33.8)* in children. 86 *(53.4%)* adults and 49 *(57%)* children were lost to follow up. As on last follow up 161 *(96.4%)* adults and 86 *(98.8%)* children were alive and 6 *(3.6%)* adults and 1 *(1.2%)* child respectively had expired.

Of the total cases of ITP, persistent and chronic cases comprised of 74 *(44.3%)* and 93 *(55.7%)* in adults, and 29 *(33.3%)* and 58 *(66.7%)* in children. After a median follow up of 18.6 months *(range:1-170)* in adults and 12 months *(range: 1-173)* in children from splenectomy, 115 *(68.9%)* adults and 63 *(72.4%)* children continued to be in response, while 48 *(28.7%)* adults & 23 *(26.4%)* children were refractory to splenectomy. Among those continuing in response, 44 *(38.2%)* adults and 25 *(39.7%)* children respectively are on follow up; while in the refractory group, those who continue to be on follow up are 31 *(64.6%)* adults and 12 *(52.2%)* children respectively. 2 (1.2%) of the adult refractory patients expired while on follow up.

In those patients who continued in response, the median duration of follow up was 11.9 *(range:1-164; mean-33.5)* & 4.5 *(range:1-173; mean-29.5)* months in adults and children respectively; while in patients with refractory ITP, the median duration of follow up was 38.7 months *(range: 1-170; mean-38.6)* in adults, and 20.1 months *(range:7-154; mean-48.3)* in children.

A. ANNUAL DISTRIBUTION OF CASES: (Fig:1)

Among the analyzed cases (n=254), the average number of splenectomy was 17 per year (11 adults and 6 children).

B. DEMOGRAPHICS OF ITP PATIENTS: (Tables: 1, 23, 25, 26)

Age: The median age at diagnosis and splenectomy of total cases were 24 *(5-64)* & 27 *(16-65)* years in adults and 8 *(2-14)* & 10 *(4-14)* years in children. Among the responders to splenectomy, the median age at diagnosis and splenectomy were 24 *(5-64)* & 26 *(15-65)* years in adults and 8 *(2-14)* & 10 years *(4-14)* in children. In refractory cases the median age were 28 *(12-60)* & 31 *(15-61)* years in adults and 7 *(2-14)* & 9 *(4-14)* years in children at diagnosis and splenectomy respectively. Younger age at diagnosis and splenectomy was found have a near statistically significant p value (0.061). In a study by Kumar S et al[1], the younger age at splenectomy was found to be a significant predictor of response.

Sex distribution: The male: female ratio was 44:123 in adults and 49:38 in children. The male: female ratio in responders and refractory were 23:92 and 19:29 in adults and 34:29 and 14:9 in children. The female preponderance observed among adult responders was found to be statistically significant *(p=0.01).* The sex distribution of cases in adults was found to be similar to other published studies, ie; Kumar S et al[1], Schwartz J et al[15], Shojaiefard A et al[76], Bourgeois E et al[77].

Phase of ITP: The persistent to chronic ITP ratio at splenectomy was 74:93 in adults and 29:58 in children. The same ratio in responders and refractory cases were 52:63 and 20:28 in adults and 26:37 and 3:20 in children. Among responders in children,

persistent phase of the disease showed a statistical significance *(p=0.019).* There is no available comparable literature for this observation.

C. PRE-SPLENECTOMY VARIABLES: (Tables 2-6, 23,25,26)

Clinical features at initial diagnosis: In both adults and children 97.6% of cases were symptomatic at the initial diagnosis.

Platelet count at diagnosis and splenectomy: The median platelet count of total cases at diagnosis was 10 x 10^9/L in both adults and children with a range of 1-65 x 10^9/L and 1-41 x 10^9/L in either group respectively. The platelet count at diagnosis was observed to be in the same range as reported in other studies.[1] The median platelet count at diagnosis showed a similar pattern in responders (adult:children =10 x 10^9/L: 9.5 x 10^9/L) and refractory (adult: children=10 x 10^9/L :10 x 10^9/L) cases. Platelet at diagnosis was not found to have any statistical correlation with the response outcome.

Auto-immune markers at diagnosis: Positive test for auto-immune markers, ie; antinuclear antibody (ANA) and direct coomb's test (DCT) were noted in 24 *(14.4%)* and 20 *(12%)* cases of adults and 7 *(8%)* and 9 *(10.3%)* cases of children respectively.

Treatments, response status, & complications at diagnosis & subsequently: Nearly all patients were treated with corticosteroids (Prednisolone, Dexamethasone or Methyl Prednisolone) at the time of initial diagnosis, ie; 99.4% of adults and 100% of children. 58.1% *(n=97)* of the adults and 54% *(n=47)* of children showed response (R/CR) to initial treatment. Comparable patterns of response to initial treatment were observed in responders *(adults: children = 66:35; 57.4%:55.6%)* & refractory *(adults: children*

=28:12; 58.3%:52.1%) cases. This is in contradiction to the observation by some workers (Kumar S et al[1] and Fabris S et al[87]).

Prior to splenectomy, 60 *(36%)* adults and 26 *(30%)* children were found to be steroid dependent and the remaining showed neither response to steroids nor multiple other treatment regimens. Among adults and children, steroid dependency in the pre-splenectomy period was observed in 40% (n=46) and 28.6% (n=18) of responders and 25% (n=12) and 34.8% (n=8) of refractory cases respectively.

Steroid related toxicities were the most observed (39 [23.3%] adults and 8 [9.1%] children) health problems during the pre-splenectomy drug treatment.

D. PERI-SPLENECTOMY VARIABLES: (Tables 7-11, 23, 25, 26)

In the immediate pre-splenectomy period, 63.5% of adults and 65.4% of children were symptomatic. 56.9% *(n=95)* adults and 47.1% *(n=41)* children received high dose dexamethasone for four days prior to splenectomy.

At splenectomy, the median platelet count of total cases was 20 $x10^9$/L (1-369 x 10^9/L) in adults and 13 x 10^9/L (1-182 x 10^9/L) in children. In majority of the cases *(34.7% adults & 36.8% children)* the platelet count was below 10 $x10^9$/L. Among those who received high dose dexamethasone therapy in the immediate pre-splenectomy period, the median platelet count was 33 $x10^9$/L & 12 $x10^9$/L respectively in adults and children. In responders & refractory cases the median platelet count at diagnosis was 30 x 10^9/L and 10 x 10^9/L in adults and 15.5 x 10^9/L & 9.3 x 10^9/L in children. In adults, the higher platelet count at splenectomy noted in responders

compared to refractory cases (30 x 10^9/L vs 10 x 10^9/L) showed statistical significance *(p=0.004)* and this is in accordance with the observation by Kumar S et al.[1] However in children, the same showed no statistical significance (*15.3 x10^9/L versus 9.3 x 10^9/L; p=0.161*).

Data on the vaccination status was available only for 132 adults and 64 children and all of them were vaccinated. The median time to splenectomy from vaccination was 35 *(0-1555)* days in adults and 28 *(1-1011)* days in children. There was no significant difference in the incidence of post splenectomy infections in the patients who received vaccination at a shorter interval of less than 10 days pre-splenectomy from those who received at more than 10 days prior to splenectomy.

The median time to splenectomy from diagnosis was 14.3 *(3-290)* months and 18.1 *(4-117)* months in adults and children respectively. The adult:child ratio of the median time to splenectomy in responders and refractory cases were 13.9:15.2 months and 15.5:27 months respectively. This is longer than the median time to splenectomy reported by other workers (Kumar S et al[1], Schwartz J et al[15], Shojaiefard A et al[76], Bourgeois E et al[77]).

Splenectomy in 90.4% *(n=151)* of adults & 96.6% *(n=84)* of children were done as elective procedure. Of these laparotomy & laparoscopy constituted 90.1% and 9.9% in adults and 94% and 6% respectively in children. Emergency splenectomy was done in 16 adults and 3 children. All *(except in 1 adult)* were done by laparotomy procedure. Intracerebral bleed was the commonest indication for emergency splenectomy *(8 adults and all 3 children)*. Other indications included uncontrolled gastrointestinal bleed and hemorrhage into cystadenoma ovary. 4 cases were done as

part of emergency surgery for other causes *(ie; pregnancy with fetal distress, acute calculous cholecystitis, carcinoma rectum and non-healing fistula in ano with abscess).* The one laparoscopic emergency splenectomy was done for IC bleed. Splenunculi were identified in 17 *(10.2%)* adults and 16 *(18.4%)* children. Among adults, splenunculi was observed in 10 responders and 7 refractory cases; while in children splenunculi was observed in 14 and 2 cases respectively. The presence of splenunculi showed no significant statistical correlation (*p=0.211 in adults & 0.323 in children*) with final outcome.

Infection (ranging from short febrile illness with no identifiable focus to frank sepsis) was the most frequent complication in the peri-operative period with an incidence of 19.2% *(n=32)* in adults and 4.6% *(n=4)* in children. 4 adults and 1 child expired in the immediate post operative period (2 adults expired due to septicaemia, and 2 adults and 1 child expired following intra-cerebral bleed). The median duration of hospital stay was 9 and 6 days in adults and children respectively. Around 50% of patients in each group received either therapeutic or prophylactic antibiotic administration during the hospital stay. There was no statistically significant difference in the duration of hospital stay among patients who underwent laparotomy or laparoscopy.

E. POST SPLENECTOMY VARIABLES: (Tables 12,23,24,25,26)

The initial response was assessed within first 56 days post splenectomy as this is the expected time of response to splenectomy, as per the current observation and recommendation.[12] 88.6% *(n=148)* of adults and 93.1% *(n=81)* of children showed initial response (R/CR) to splenectomy. The median time to response was 1 day in both

groups with a mean and range of 5.4 & 1-54 days in adults, and 3.6 & 1-28 days in children respectively. The median time to initial post splenectomy response in responders and refractory cases were 1 day *(range:1-55)* & 3 days *(range:1-60)* in adults, and 1day *(range:1-28)* & 3 days *(range:1-61)* days in children. The shorter time to response observed among responders compared to the refractory cases showed a statistical significance *(p=0.031)* in adults. Among the 148 *(88.6%)* adults and 81 *(93.1%)* children who were initial responders, 10 adults and 4 children subsequently lost response during the first 2 months post splenectomy. It is possible that the initial response noted in these patients might have been the effect of the peri-splenectomy treatment received. At 2 months post splenectomy, 82.6% adults and 88.5% children were in response; and at last follow up 115 *(68.9%)* adults and 63 *(72.4%)* children showed a response, while 48 *(28.7%)* adults & 23 *(26.4%)* children were refractory to splenectomy.

Most of the patients who were steroid dependent in the pre-splenectomy period, 76.7% [46 out of 60 cases] of adults and 69% [18 out of 26 cases] of children responded to splenectomy. This observation however was not statistically significant *(p=0.071 in adults, p=0.842 in children).*

The median peak post splenectomy platelet count observed were 306 x 10^9/L *(1-1831 x 10^9/L)* and 292 x 10^9/L *(5-2161 x 10^9/L)* for adults and children respectively. The median time to peak platelet count was 7 days in both groups with the range of 1-56 and 1-50 days respectively in adults and children. The median peak post splenectomy platelet count among responders and refractory cases were 400 x 10^9/L *(30-1831 x 10^9/L)* & 125 x 10^9/L *(1-1406 x 10^9/L)* in adults, and 335 x 10^9/L (*45-2161 x 10^9/L)* & 139 x 10^9/L *(5-1738* x *10^9/L)* in children. The median time to peak platelet

count was 7 days each in responders and refractory cases in adult as well as in children. The median peak platelet count was similar to the observation by Shojaiefard et al [76]. As observed by Kumar s et al[1] and Shojaiefard et al,[76] the higher peak platelet count was found to be a significant predictor of response both in adults *(p=0.000)* and children *(p=0.001).*

Among the initial responders, 94.6% *(n=140)* of adults and 98.8% *(n=80)* of children achieved response without any additional drug treatment. 8 adults achieved response status while on treatment with additional drugs (steroid *(n=3),* danazol + steroid *(n=1),* azathioprine ± steroid *(n=3)* and cyclosporine + steroid *(n=1)*), which were continued for more than 2 months post splenectomy. One child achieved response status while on treatment with azathioprine. All these cases who responded while on additional drug treatment, subsequently lost their response (1 adult lost response within 2 months and the rest after 2 months post-splenectomy), and were eventually grouped as refractory ITP. Among the initial responders, 33 *(22.2%)* adults and 18 *(22.2%)* children subsequently lost response, and the median time to loss of response was 8.8 *(1-108)* months in adults and 5.9 *(1 -116)* months in children. In adults, majority (63.6%; n=21) of the 'loss of response' was observed in the first year post splenectomy; while in children, only 7 out of the 18 (39%) cases showed loss of response in the first year post splenectomy. The time to loss of response observed is in concordance with that reported by Kumar S et al[1] and Shojaiefard et al.[76]

F. LAPAROSCOPY VERSUS LAPAROTOMY SPLENECTOMY: (Table.13)

A comparison of the pre and post splenectomy variables showed no statistically significant difference in the mean duration of hospital stay, time to initial response to splenectomy, number of initial responders, number of post splenectomy

loss of response or early and late post splenectomy complications, among those who underwent laparotomy and laparoscopy.

G. REFRACTORY ITP: (Tables 14-19)

To evaluate the response to treatment, the patients were divided into arbitrarily defined response groups depending on the type of drugs they received throughout.

Group 0: Not received any treatment; patients who attained response in this group were categorised as spontaneous remission or remission of uncertain origin[12].

Group 1: Patients who received treatment with steroids alone (Prednisolone, pulsed high dose dexamethasone).

Group 2: Patients treated with Dapsone, danazol or azathioprine, either alone or in combination, with or without steroids.

Group 3: Patients who received Cyclophosphamide, Cyclosporine, Mycophenolate or Vincristine, either alone or in combination, with or without Group 1& 2 Drugs

Group 4: Patients on alternative medicines (ie; Homeopathic, Siddha or Ayurvedic medicines).

Treatment and Response of refractory cases: Of the 48 adults and 23 children with refractory ITP, 38 *(79.2%)* adults and 21 *(91.3%)* children attained response to drug treatment at some point of time, but only 25 *(52.1%)* adults and 16 *(69.6%)* children respectively were in response status at last follow up. Among the cases who were in response at last follow up, 64% of adults (*n=16)* and 62.5% of children (*n=10*) belonged to the treatment group 2. The median cumulative duration in response *(total*

time in response throughout the follow up period, ie; duration in response on drug + duration in response off drug) for those who were in response at last follow up was 34 months *(range:9-145)* in adults and 47 months *(range:2-118)* in children.

Of those who responded to treatment, 14 *(56%)* adults and 10 *(62.5%)* children were off treatment as on last follow up, and 11 *(44%)* adults and 6 *(37.5%)* children continue to be on treatment. One child who belonged to group 0 responded (spontaneous remission) [12] one year after splenectomy *(platelet count at last follow up- 50 x 10^9/L, ie at 1 year 10 months post splenectomy).*

The drugs to which these patients responded post splenectomy were compared to the drugs they had shown response to at any point of time during the pre-splenectomy period. Of the refractory cases who were in response, 60% *(n=15)* of adults and 68.7% *(n=11)* of children responded to steroid based therapy. It was observed that those patients who showed pre-splenectomy response to steroid continued to be responsive to steroid in the post splenectomy period also. All the steroid dependent adults continued to be steroid dependent, whereas only 1 out of 3 continued to be steroid dependent among children.

Among the refractory cases in response, 24% *(n=6)* of adults and 12.5% *(n=2)* of children showed response to Dapsone alone; while only 1 adult case among them had shown response to Dapsone in the presplenectomy period. 12% *(n=3)* of adults and 12.5% *(n=2)* of children showed response to azathioprine alone; none among them had shown response to azathioprine in the pre-splenectomy period. The number of cases however is insufficient for a statistical correlation to be done.

Final outcome of refractory cases versus phase of ITP: Among the refractory cases who responded subsequently to drug treatment, 15 cases each of adults *(31.3%)* and children *(65.2%)* were in chronic phase of the disease at splenectomy, while only 10 *(20.8%)* adults and 1 *(4.4%)* child were in the persistent phase. These observation showed no statistical significance *(p=0.211).*

Clinical status of refractory cases at last follow up: Among those who were with 'no-response' at last follow up, 70% *(n=7)* adults and 50% *(n=1)* of children were asymptomatic at last follow up; while those who were in 'loss of response', 54% *(n=7)* adults and 20% *(n=1)* children respectively were asymptomatic.

H. POST SPLENECTOMY MORBIDITY AND MORTALITY: (Tables 20,21)

Post splenectomy health problems: Post splenectomy complications observed more frequently in adults than in children was possibly because the adults were more in number than children (*167 adults vs 87 children*). Infections *(short febrile episodes or septicaemia)* were reported in 34 *(20.5%)* adults and 7 *(8%)* children. Major post splenectomy sepsis was documented among 5 adults; 2 cases were in the early post splenectomy period (out of which 1 expired), and 3 cases (1 responder, 2 refractory cases) had late post splenectomy sepsis (out of which one refractory case expired following severe gram negative sepsis and gastrointestinal bleed at 16 months post splenectomy). Among the 2 children (refractory cases) who developed major post splenectomy sepsis, 1 was in the early post operative period and the other one child had 2 episodes of late sepsis with hypotension.

Other health problems encountered were deep vein thrombosis *(2 adults; one of them had pulmonary embolism)*, coronoary artery thrombosis *(1 adult),* and thrombocytosis *(occlusive vasculitis of the left eye was seen in an adult with platelet count 645* x *10^9/L and one child had asymptomatic thrombocytosis of 541*x *10^9/L).* A few of the patients presented with certain malignancies while on follow up, ie; mantle cell lymphoma *(1 adult responder at 2 years 8 months post splenectomy),* follicular lymphoma *(1 adult responder at 11 years 4 months post splenectomy)*, carcinoma of breast *(1 adult refractory case at 10 years post splenectomy),* and adenocarcinoma of stomach *(1 adult responder at more than 1 year post splenectomy).* 2 adults developed mixed connective tissue disorder *(after 1 year of splenectomy)* and one child developed autoimmune myocarditis with transient ischemic attack after 10 years of splenectomy. 3 adults with refractory ITP developed intracranial bleed, and one of them expired due to the same at 19 months post splenectomy. Incidence of venous thrombosis is in concordance with that reported by Schwartz et al[15].

Mortality: Total deaths were 6 *(3.6%)* in adults and 1 *(1.2%)* in children. The median time to death was 12 days *(range:1-38)* in adults and 1 day in children. 4 adults and the 1 child expired in the early post splenectomy period. The cause of death was intra-cerebral bleed in 2 adults and the 1 child. Death was due to sepsis in the third adult patient and sepsis with intra-cerebral bleed in the fourth. 2 cases of late mortality were in adult females in the refractory group. One lady expired at 16 months post splenectomy following severe gram negative sepsis with massive gastro-intestinal bleed & the second case expired at 19 months post splenectomy following intra-cerebral bleed. Similar mortality pattern has been reported by Swartz et al[15] & Bourgeois et al[77].

I. SURVIVAL CHARACTERISTICS: (Table 22)

As on last follow up, 161*(96.4%)* adult patients were alive and 75 *(46.6%)* among them were on follow up. Among children, 86 *(98.8%)* were alive with 37 *(43%)* being on follow up. In responders, the mean duration of follow up was 33.5 months *(median: 11.9, range: 1-164)* in adults and 29.5 months *(median: 4.5, range:1-173)* in children. For refractory cases it was 38.6 months *(median: 38.7, range:1-170)* in adults and 48.3 months *(median:20.1, range:7-154)* in children.

The 5 year and 10 year overall survival was 96.9 ± 1.6% & 93.4 ± 3% in adults and 98 ± 1.6% & 98 ±1.6% in children respectively. The 5 and 10 year event free survival was 75.2 ± 3.7% & 71.5 ± 4.5% in adults and 79.1 ± 4.6% and 70 ±7.5% in children respectively. These observations are similar to that reported by Kumar S et al[1] and Schwartz et al[15].

J. PROGNOSTIC DETERMINANTS AND LITERATURE COMPARISON:

Analysis in adults showed that higher median platelet count at splenectomy (*p=0.004*), female sex (*p=0.011*), shorter median time to initial response to splenectomy *(p=0.031)* and higher median peak post splenectomy platelet count *(p=0.000)* observed in responders as compared to refractory cases are statistically significant. In adults, the younger age at diagnosis and splenectomy was observed to have near statistically significant p value *(p=0.061)*. Comparison with published data showed a similar observation for platelet count at splenectomy, peak post splenectomy platelet count (Kumar S et al[1], Bourgeois et al[77], Shojaiefard et al[76]), younger age at splenectomy (Kumar S et al[1]) and female sex (Bourgeois et al[77]).

Among responders in children, higher median peak post splenectomy platelet count *(p=0.001)* and persistent phase of the disease *(p=0.019)* were observed to be statistically significant. There is no available comparable literature for the observations in children.

The observations and the prognostic determinants analyzed in the present study are compared with the available literature in the tables that ensues (tables: 25,26).

Table. 25. Splenectomy for persistent and chronic ITP in adults and children: a comparison of present study and literature

Variables (adult/child)	Present study		Schwartz et al[15]	KumarS et al[1]	Bourgeois et al[77]	
	Adults	Children	Adults	Adults	Adult+child	Child
Time period (duration in years)	1995-2009(15)		1988-1993(5)	1985-1998(14)	1985-1994(10)	
Number of patients	167	87	56	140	183(158+25)	25
Male:Female	44:123	49:38	11:45	58:82	66:117	--
Persistent: chronic	74:93	29:58	--	--	--	--
Platelet at diagnosis ($1x10^9$/L) $	10 (1-65)	10 (1-41)	--	15 (1-95)	--	--
Age at splenectomy (years) $	27 (16-65)	10(4-14)	37 (15-81)	56(18-90)	--	--
Response to initial treatment#	148 (88.6%)	81 (93.1%)	--	--	--	--
Platelet at splenectomy($1x10^9$/L) $	20(1-369)	13(1-182)	14.5(2-90)	46.5(1-266)	--	--
Time to splenectomy (months) $	14.3(3-290)	18.1(3.1-117)	12 (0.5-233)	7.5(0-26)	--	--
Laparotomy:Laparoscopy	151:16	82:5	--	--	--	--
Splenunculi#	17(10.2)	16 (18.4)	6 (11%)	--	--	--
Initial responders [CR/R] #	148(88.6%)	81(93.1%)	48 (86%)	123(88%)	159(87%)	--
Time to initial response(R/CR)-days$	1(1-54)	1(1-28)	--	--	--	--
Peak post splenectomy platelet$	306(1-1831)	292(5-2161)	--	--	--	--
Time to peak platelet (days) $	7(1-56)	7(1-50)	--	--	--	--
Initial Non-responders#	15(9%)	5(5.7%)	8 (14%)	17(12.1%)	24(13%)*	2(8%)
Post operative deaths#	4 (2.4%)	1(1.2%)	--	2(1.4%)	0	--
Subsequent loss of R#	33(22.2%)	18(22.2%)	11(19.6%)	22(15.7%)	29(16%)	5(20%)
Time to loss of R (months) $	8.8(0.4-108)	5.9(0.4-116)	**4-8.5 yrs**	3(1-38)	--	--
Total Refractory cases #	48(28.7%)	23(26.7%)	19 (34%)	39(27.9%)	53(29%)	--
Total patients in response [R/CR] #	115(68.9%)	63(72.4%)	37 (63%)	--	--	--
Refractory cases responded Rx#	25(52%)	16(69.6%)	5	8(20.5%)	42(79%)	6(24%)
Refractory in spontaneous remission#	0 (0%)	1(1.2)	--	--	4(2.2%)	--
Follow up of total cases (months)$	38.9 (mean)	33.8 (mean)	--	37.5(0-183)	--	--
Follow up of responders$	11.9(0.2-164)	4.5(0.2-172.7)	7.5yrs (5-10.5)	--	--	--
Follow up of refractory cases$	38.7(0.2-169.3)	20.1(6.8-153.7)	--	--	7.5(5-15)yrs	--
Post splenectomy thrombosis$	3 (1.8)	0(0)	--	5.7%	--	--
OS of responders$	100%	100%	---	--	--	--
OS of refractory cases $	94.7%±3.7%	100%	--	--	--	--
5 year EFS# of total cases	75.2 %± 3.7%	79.1 ± 4.6%	--	75%	--	--
Total number of death#	6 (3.6%)	1(1.2%)	0 (0%)	25(17.9%)	--	--

n (%); $ median (range) * 14 (10%) had transient response

Table. 25. Splenectomy for persistent & chronic ITP in adults and children: a comparison of present study & literature contd..

Variables (adult/child)	Present study		Mc Millan R et al[2]	Shojaiefard et al[76]
	Adults	Children	Adult refractory cases	Adults
Time period (duration in years)	1995-2009(15)		1986-1998 (13)	2002-2004(2)
Number of patients	167	87	114	31
Male:Female	44:123	49:38	41:73	10:21
Persistent: chronic	74:93	29:58	--	--
Platelet at diagnosis ($1x10^9$/L) $	10 (1-65)	10 (1-41)	--	--
Age at splenectomy (years) $	27 (16-65)	10(4-14)	37 ±18.4 yrs	33
Response to initial treatment#	148 (88.6%)	81 (93.1%)	--	22
Platelet at splenectomy($1x10^9$/L) $	20(1-369)	13(1-182)	--	22
Time to splenectomy (months) $	14.3(3-290)	18.1(3.1-117)	3-120	5(1-120)
Laparotomy:Laparoscopy	151:16	82:5	--	--
Splenunculi#	17(10.2)	16 (18.4)	--	3
Initial responders [CR/R] #	148(88.6%)	81(93.1%)	75 (74.1%)	29(93%)
Time to initial response(R/CR)-days$	1(1-54)	1(1-28)	--	--
Peak post splenectomy platelet$	306(1-1831)	292(5-2161)	--	307(±199)
Time to peak platelet (days) $	7(1-56)	7(1-50)	--	--
Initial Non-responders#	15(9%)	5(5.7%)	23	2(7%)
Post operative deaths#	4 (2.4%)	1(1.2%)	--	--
Subsequent loss of R#	33(22.2%)	18(22.2%)	--	5
Time to loss of R (months) $	8.8(0.4-108)	5.9(0.4-116)	--	6
Total Refractory cases #	48(28.7%)	23(26.7%)	98	5
Total patients in response [R/CR] #	115(68.9%)	63(72.4%)	51 (48.6%)	26
Refractory cases responded Rx#	25(52%)	16(69.6%)	--	1
Refractory in spontaneous remission#	0 (0%)	1(1.2)	--	--
Follow up of total cases (months)$	38.9 (mean)	33.8 (mean)	--	--
Follow up of responders$	11.9(0.2-164)	4.5(0.2-172.7)	--	--
Follow up of refractory cases$	38.7(0.2-169.3)	20.1(6.8-153.7)	--	--
Post splenectomy thrombosis$	3 (1.8)	0(0)	--	--
OS of responders$	100%	100%	--	--
OS of refractory cases $	94.7%±3.7%	100%	--	--
5 year EFS# of total cases	75.2 %± 3.7%	79.1 ± 4.6%	--	--
Total number of death#	6 (3.6%)	1(1.2%)	--	--

#- n (%); $- median (range) ^14 (10%) had transient response

Table. 26. **Prognostic determinants of splenectomy outcome- responders versus refractory cases (present study and literature)**

Variables (adult/child)	Present study				Schwartz et al[15]		Kumar S et al[1]	
	Adults	**p**	**Children**	**p**	**Adults**	**p**	**Adults**	**p**
Univariate analysis								
Time period(duration in years)	1995-2009(15)	--		--	1988-1993(5)	--	1985-1998(14)	--
Number of patients	167	--	87	--	56	--	140	**--**
Male:Female	23:92 vs 19:29	**0.011**	34:29 vs 14:9	0.631	11:45	0.218	58:82	**--**
Persistent: chronic	52:63 vs 20:28	0.731	26:37 vs 3:20	**0.019**	--	--	**--**	**--**
Platelet at diagnosis ($1x10^9$/L) $	10 vs 10	0.882	9.5 vs 10	0.371	--	--	15 (1-95)	--
Age at splenectomy (years) $	26 vs 31	**0.061**	10 vs 9	0.411	37 (15-81)	0.074	51 vs 73	**<0.001**
Response to initial treatment at diagnosis#	57.4% vs 58.3%	0.723	55.6& vs 52%	0.921	--	--	91% vs 76%	**0.03**
Platelet at splenectomy($1x10^9$/L) $	30 vs 10	**0.004**	15.5 vs 9.3	0.161	14.5(2-90)	--	59 vs 27	**0.008**
Time to splenectomy (months) $	13.9 vs 15.5	0.757	15.2 vs 27	0.871	12 (0.5-233)	0.397	7.5(0-26)	--
Laparotomy:Laparoscopy	104:11 vs 43:5	1.000	59:4 vs 22:1	1.000	--	--	--	--
Splenunculi	10 vs 7	0.211	14 vs 2	0.323	6 (11%)	--	--	--
Time to initial response(R/CR)-days$	1 vs 3	**0.013**	1 vs 3	0.138	--	--	--	--
Peak post splenectomy platelet($1x10^9$/L) $	400 vs 125	**0.000**	335 vs 139	**0.001**	**--**	**--**	385 vs 135	**0.001**
Time to peak platelet (days) $	7 vs 7	0.152	7 vs 7	0.755			--	--
Multivariate analysis:								
Higher peak platelet count	--	--	--	--	--	--	**--**	**0.007**
Younger age	--	--	--	--	---	--	**--**	**0.03**

#: n (%); $: median (range)

Table. 26. Prognostic determinants of splenectomy outcome (present study and literature) contd...

Variables (adult/child) Univariate analysis	Present study				Bourgeois et al[77]		Shojaiefard et al[76]		Fabris et al[87]	
	Adults	p	Children	p	Adult/child	p		p	Adult+child	p
Time period(duration in years)	1995-2009(15)	--	--	--	1985-1998(14)	--	2002-2004(2)	--	--	--
Number of patients	167	--	87	--	140	--	31	--	61	--
Male:Female	23:92 vs 19:29	**0.011**	34:29 vs 14:9	0.631	53%:69% vs 47%:31%	**0.07**	9:17 vs 1:4	NS	12:24 vs 8:10	0.60
Persistent: chronic	52:63 vs 20:28	0.731	26:37 vs 3:20	**0.019**	--	--	--	--	--	--
Platelet at diagnosis ($1x10^9$/L) $	10 vs 10	0.882	9.5 vs 10	0.371	--	--	22 vs 19	NS	--	--
Age at splenectomy (years) $	26 vs 31	**0.061**	10 vs 9	0.411	35 vs 39	0.10	--	--	31 vs 41	0.19
Response to initial treatment at diagnosis#	58.4% vs 58.4%	0.723	55.6& vs 52%	0.921	--	--	--	--	88% vs 12%	--
Platelet at splenectomy($1x10^9$/L) $	30 vs 10	**0.004**	15.5 vs 9.3	0.161	33 vs 25	0.07	--	--	--	--
Time to splenectomy (months) $	13.9 vs 15.5	0.757	15.2 vs 27	0.871	--	--	--	--	--	--
Laparotomy:Laparoscopy	104:11 vs 43:5	1.000	59:4 vs 22:1	1.000	--	--	--	--	--	--
Splenunculi	10 vs 7	0.211	14 vs 2	0.323	--	--	--	--	--	--
Time to initial response(R/CR)-days$	1 vs 3	**0.013**	1 vs 3	0.138	--	--	--	--	--	--
Peak post splenectomy platelet($1x10^9$/L) $	400 vs 125	**0.000**	335 vs 139	**0.001**	650 vs 346	**<0.001**	307 vs 309	NS	--	--
Time to peak platelet (days) $	7 vs 7	0.152	7 vs 7	0.755	--	--	--	--	--	--
Multivariate analysis:										
Higher peak platelet count$:	--	--	--	--	--	--	--	--	--	--
Younger age	--	--	--	--	--	--	--	--	--	--
Platelet at 1 month after splenectomy$:	--	--	--	--	--	--	328 vs 171	NS	--	--
Platelet at 3 month after splenectomy$:	--	--	--	--	--	--	275 vs 159	NS	--	--
Platelet at 6 month after splenectomy$:	--	--	--	--	--	--	262 vs 68	**<0.05**	--	--
Platelet at 12 month after splenectomy$:	--	--	--	--	--	--	262 vs 32	**<0.01**	--	--
Platelet at 24 months after splenectomy$:	--	--	--	--	--	--	261 vs 35	**<0.01**	--	--

#: n (%); $: median

LIMITATIONS OF THE STUDY :

1. **Retrospective analysis:** As majority are retrospective cases, the clinical, laboratory, and follow up parameters in the required detail could not be obtained for all cases due to incomplete documentation or missing documents.
2. **Follow up:** One of the limitations to data interpretation is the fact that more than 50% cases (53.4% in adults and 57% in children) are lost to follow up, with 52 (31%) adults and 29 (33.3%) children lost to follow up within one year, and 72 (43%) adults and 44 (50.5%) children lost within 5 years post splenectomy.
3. **Change in the terminologies and definitions:** The present study is analyzed according to the new recommendations and definitions put forth by the international working group (IWG),[12] applied to a cohort diagnosed and treated as per the old definitions, terminologies and outcome criteria.
4. **Comparable clinical trials:** Comparable studies analyzed according to the new recommendation are lacking.

CONCLUSIONS:

Splenectomy has the potential to provide long-term control of disease in adults and children with ITP who have failed to respond to steroid therapy or who are steroid dependant. The procedure is associated with low morbidity and minimal mortality; and nearly two-thirds of patients (adults and children) undergoing splenectomy for ITP can be expected to have long-term control of their disease. In patients who are in persistent phase of the disease and no life threatening bleeding, drug trial may be tried for a reasonable period (at least 12 months) before resorting to splenectomy. Most of the loss of responses occurs within first year after splenectomy. Although certain pre and post splenectomy variables (ie; females, higher platelet count at splenectomy and peak post splenectomy platelet count), shows significant correlation with response, this needs further analysis to ascertain the predictive value of the variables associated with the response. In patients who fail to respond or who have a loss of response after splenectomy, adequate control of the disease can often be achieved to some extent with various therapeutic maneuvers. Corticosteroids should be the first line of therapy for these patients because the rate of response is high, even among those who were refractory to corticosteroids before splenectomy. Other agents that can be of benefit include Dapsone, immunosuppressive agents mainly Azathioprine and Mycophenolate and Danazol. Life threatening post splenectomy sepsis is an infrequent long term complication of the procedure.

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APPENDIX- I

REFRACTORY ITP TREATMENT GROUPS (description)			
Groups	**Drugs**	**Adults**	**Children**
Group 0	Nil (No Treatment)	4	2
	Total cases	**4**	**2**
Group 1	**Steroid Alone**		
	Prednisolone	4	2
	Dexamethasone	2	1
	Total cases	**6**	**3**
Group 2	**Dapsone/Azathioprine/Danazol ±Steroid:**		
	Dapsone Alone	8	2
	Dapsone+Steroid	4	5
	Azathioprine Alone	5	2
	Azathioprine+Steroid	6	2
	Dapsone+Azathioprine+Steroid	3	1
	Prednisolone,Dapsone,Danazol	0	1
	Prednisolone,Dapsone,Azathioprine,Danazol	1	1
	Total cases	**27**	**14**
Group 3	**Combination Treatment: Cyclophosphamide/CSA/MMF/VCR ± Group 1& 2 Drugs**		
	Prednisolone,Dapsone,MMF*	1	0
	Prednisolone,Cyclophosphamide	1	0
	Pulse Dexa,Dapsone,MMF,CSA*	1	0
	Prednisolone,Azathioprine,MMF	0	1
	Prednisolone,Dexamethasone,Dapsone,Azathioprine, MMF, CSA,Cylophosphamide,VCR*	0	1
	Prednisolone,Dapsone,Azathioprine, Cyclophosphamide	3	0
	Prednisolone,CSA	1	0
	Prednisolone,Dexamethasone,Dapsone,Azathioprine, Danazol,CSA,IVIG,VCR	1	0
	Danazol,MMF	1	0
	Prednisolone, Dapsone, Azathioprine,MMF, CSA	0	1
	Total cases	**9**	**3**
Group 4	**Alternative Treatment:** (Homeopathic, Siddha, Ayurvedic medicines)	**2**	**1**
	Total cases	**2**	**1**

*MMF=Mycophenolate, CSA=Cyclosporine A, VCR=Vincristine

APPENDIX- II

DOSAGE OF THE DRUGS USED		
Sl.No	**Drugs**	**Dosage**
1	Prednisolone	1-2mg/Kg/day
2	Dexamethasone	0.8/Kg/day
3	Dapsone	100mgin adults; 1.5mg/Kg/day in children
4	Azathioprine	1-2 mg/kg/day
5	Danazol	200mg 3-4 times daily
6	Cyclophosphamide	1g every 3-4 weeks x 4 doses
7	Mycophenolate	500mg -1g twice daily
8	Cyclosporine A	2.5mg/Kg twice daily
9	Vincristine	1.4mg/m^2 every week x 4 doses
10	IVIG	1g/Kg x 2 days

PROFORMA:

Title: Splenectomy for children and adults with persistent and chronic immune thrombocytopenia: long term results

Sl.No:

Name: Hospital No: Sex:

Age at diagnosis: Date of diagnosis:

Age at splenectomy**:** Date of splenectomy**:**

A. Pre-splenectomy clinical and laboratory parameters:

1. Phase of ITP : 2. Symptoms:

3. Platelet count: 4. Auto-immune markers:

5. Viral markers: 6. Bone marrow findings:

7. Co-morbidities: 8. Initial treatment:

9. Response to initial treatment: 10.Subsequent treatment:

11. Response to subsequent treatment:

12. Total number of presplenctomy loss of response:

13. Health problems during pre-splenectomy treatment:

B. Perisplenectomy variables:

1. Pre-splenectomy status (Steroid dependent/not responsive to steroid or multiple agents):
2. Peri-splenectomy symptoms:
3. Date of vaccination:
4. Peri-splenectomy treatment (including Platelet transfusions):
5. Pre-splenectomy platelet count:
6. Date of splenectomy
7. Nature of splenectomy: Emergency/Elective (if emergency, indication)
8. Type of splenectomy: Laparotomy/Laparoscopy

9. Place of splenectomy: CMC/outside
10. Splenunculi: Yes/No
11. Spleen HPR:
12. Immediate post splenectomy complications:
13. Antibiotic requirement:
14. Number of hospital stay:

C. Post splenectomy variables:

1. Post splenectomy platelet count at 24hrs, 72hrs, 7 days, 14 days, 1 month, 2 months, 3 months, 6 months, 9months, 1 year, 2 years, 3 yrs, 5yrs, 10yrs, 15yrs.
2. Post splenectomy treatments: (drug/drugs, duration, response)
3. Type of initial response (R/CR/NR)
4. Date of initial response:
5. Peak post splenectomy platelet count & the date of Peak platelet count:
6. Response status at 2 months (56 days) post splenectomy;:
7. Dates of subsequent loss of responses:
8. Treatments at loss of responses (drug/drugs, duration, response)
9. Total number of post splenectomy loss of responses:

D. Follow up and final response status:

1. Date of last follow up:
2. Platelet count at last follow up:
3. Response status at last follow up (responder/refractory; if refractory whether in response to treatment or not):

4. Treatment at last follow up (if on treatment, the type, time since when on treatment, steroid dependency?)
5. If in response at last follow up, date since when in response
6. If not in response, whether symptomatic or not, date of last loss of response
7. If dead, date and cause of death
8. Post splenectomy health problems (including post splenectomy sepsis):
9. Follow up status (on/lost).

Sample of follow up letter & form:

Vellore

Date:

Dear Mr. / Ms. _____,

Our records show that you / your child, _____, CMC No: _____, underwent splenectomy (removal of the spleen) in this hospital in _____, _____. (month / year).

We are analysing the response to treatment of all patients with Immune thrombocytopenia (ITP), who underwent splenectomy in this hospital. We therefore request you to provide your / your child's current status as per the form attached to this letter. Please send the information back to us at the earliest in the self addressed envelope provided or by email in the id; haemat@cmcvellore.ac.in

Thanking you,

Dr.Alok Srivastava,
Professor& HOD,
Department of Hematology,
Christian Medical College,
Vellore, Tamilnadu-632004. India.

FORM-1 (2009)

Name:
Hosp No:

1. What are you doing at present? Working ☐ Studying ☐ At home ☐

2. What are the medications you have taken after the last visit to CMCH & for how long?

Medicine				
Duration (from …to …)				

4. Are you on any medications at present? Yes ☐ No ☐

If yes, kindly specify the medicine and for how long you have been taking it;

Medicine:

Duration (from… to..):

3. Details of blood tests done after the last visit to CMCH:

Date						
Platelet count						

6. With regard to your current health status kindly tick the appropriate box:

Bleeding problems at present: Yes ☐ No ☐

Site of bleeding: Gums ☐ Nose ☐ Skin ☐ Menstrual ☐

Alive: ☐ Dead: ☐

7. If not alive;

When was the date of demise? ……..

What was the cause of death? ……..…….

We request you to send us with your most up to date contact information.

Kindly include:

Postal address:
Telephone number:
Mobile number:
E-mail address:

We look forward to seeing you on your next visit and would request you to send us information on your current status every year for our records using this form.

Warm regards,

Dr.Alok Srivastava

BIBLIOGRAPHY:

1. Kumar S, Diehn FE, Gertz MA, Tefferi A. Splenectomy for immune thrombocytopenic purpura: long-term results and treatment of postsplenectomy relapses. *Ann Hematol*.2002;81:312–319
2. McMillan R, Durette C. Long-term outcomes in adults with chronic ITP after splenectomy failure. *Blood*. 2004;104:956-960.
3. Vesely SK, Perdue JJ, Rizvi MA,Terrell DR, George JN. Management of adult patients with persistent idiopathic thrombocytopenic purpura following splenectomy; a systematic review. *Ann Intern Med.* 2004;140:112-12
4. Duperier T, Brody F, Felsher J, Walsh RM, Rosen M, Ponsky J. Predictive factors for successful laparoscopic splenectomy in patients with immune thrombocytopenic purpura*. Arch Surg*. 2004;139:61-66.
5. Akwari OE, Itani KMF, Coleman RE, Rosse WF. Splenectomy for primary and recurrent immune thrombocytopenic purpura (ITP) current criteria for patient selection and results. *Ann. Surg*.1987;206:529-539.
6. Law C, Arcaccio MM, Tam P, Heddle N, Elton JG. High-dose intravenous immune globulin and the response to splenectomy in patients with idiopathic thrombocytopenic purpura. *N Egl J Med*.1997;336:1494-8.
7. Supe A, Parikh M, Prabhu R, Kantharia C, Farah J. Post-splenectomy response in adult patients with immune thrombocytopenic purpura. *Asian J Transf Sci*. 2009; 3(1): 6-9.
8. Mikhael J**,** Kessler CM, Danese M, Deuson R. Initial & Long-term outcomes of splenectomy in adult immune thrombocytopenic purpura **(**itp**)** patients: a systematic review and meta-analysis. *Blood* (ASH Annual Meeting Abstracts) 2007; 110: Abstract 1321.

9. Dolan JP, Sheppard BC, Deloughery TG. Splenectomy for immune thrombocytopenic purpura: surgery for the 21st century. *Am. J. Hematol*. 2008;83:93-96.
10. Jacobs P, Wood L. Emergency surgery and refractory immune thrombocytopenic purpura. *S Air Med J.* 1986; 69: 321-322.
11. Kojouri K, Vesely SK, Terrell DR, George JN. Splenectomy for adult patients with idiopathic thrombocytopenic purpura: a systematic review to assess long-term platelet count responses, prediction of response, and surgical complications. *Blood*. 2004; 104:2623-2634.
12. Rodeghiero F, Stasi R, Gernsheimer T, Michel M, Provan D, Arnold DM, Bussel JB, Cines DB, Chong BH, Cooper N et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. *Blood*. 2009;113:2386-2393
13. Kang CM, Lee JG, Kim KS, Choi JS, Lee WJ, Kim BR, Ko YW, Han JS, Min YH. Long-term follow-up of laparoscopic splenectomy in patients with immune thrombocytopenic purpura. *J Korean Med Sci.* 2007; 22: 420-4
14. Keidar A, Sagi B, Szold A. Laparoscopic splenectomy for immune thrombocytopenic purpura in patients with severe refractory thrombocytopenia. *Pathophysiol Haemost Thromb*. 2003;33:116–119
15. Schwartz J, Leber MD, Gillis S, Giunta A, Eldor A, Bussel JB. Long term follow-up after splenectomy performed for immune thrombocytopenic purpura (ITP). *Am. J. Hematol*.2003; 72:94-98.
16. Neunert CE, Buchanan GR, Imbach P, Bolton-Maggs PHB,. Bennett CM, Neufeld EJ, Vesely SK, Adix L, Blanchette VS, Ku¨hne T, for the

Intercontinental Childhood ITP Study Group Registry II Participants. Severe hemorrhage in children with newly diagnosed immune thrombocytopenic purpura. *Blood*. 2008;112:4003-4008

17. Panitsas FP, Theodoropoulou M, Kouraklis A, Karakantza M, Theodorou GL, Zoumbos NC, Maniatis A, Mouzaki A. Adult chronic idiopathic thrombocytopenic purpura (ITP) is the manifestation of a type-1 polarized immune response. ***Blood.*** 2004; 103:2645-2647.
18. Semple JW, Allen D, Rutherford M, Woloski M, David M, Wakefield C, Butchart S, Freedmand J, Blanchette V and the Canadian Children's Platelet Study Group (CCPSG). Anti-D (winrho SD^{TM}) treatment of children with chronic autoimmune thrombocytopenic purpura stimulates transient cytokine/chemokine production. ***Am. J. Hematol***. 2002; 69:225-227.
19. Bussel JB, Graziano JN, Kimberly RP, Pahwa S, Aledort LM. Intravenous Anti-D treatment of immune thrombocytopenic purpura: analysis of efficacy, toxicity, and mechanism of effect. ***Blood.*** 1991; 77:1884-1893
20. Nugent DJ. Immune thrombocytopenic purpura of childhood. *Hematology*. 2006;97-103
21. Beardsley DS. ITP in the 21st Century. *Hematology*. 2006;402-407
22. Chong BH, Ho S-J. Autoimmune thrombocytopenia. ***J Thromb Haemost.*** 2005; 3: 1763–72.
23. Wang T, Zhao H, Ren H, Guo J, Xu M, Yang R, Han ZC. Type 1 and Type 2 T-cell profiles in idiopathic Thrombocytopenic purpura. *Haematologica*. 2005; 90:914-923
24. Cooper N, BusseL JB. The pathogenesis of immune thrombocytopenic purpura. *Br J Haematol*. 2006;133:364-374

25. Coopamah MD, Garvey MB, Freedman J, Semple JW. Cellular immune mechanisms in autoimmune thrombocytopenic purpura: an update. *Transfus Med Rev.2003;* 17: 69-80

26. Provan D. Characteristics of immune thrombocytopenic purpura: a guide for clinical practice. *Eur J* Ha*ematol.* 2009; (Suppl 71):8-12

27. Stevens W, Koene H, Zwaginga JJ, Vreugdenhil G. Chronic idiopathic thrombocytopenic purpura: present strategy, guidelines and new insights. *Netherlands The journal of medicine*; 2 0 0 6; 6 4:356-363.

28. Davies JM, Barnes R, Milligan D. Update of guidelines for the prevention and treatment of infection in patients with an absent or dysfunctional spleen. *Journal of the Royal College of Physicians of London. Guideline up-date* 2002;2:440-443 .

29. Psaila B, Bussel JB. Immune thrombocytopenic purpura. *Hematol Oncol Clin N Am.* 2007; 21:743-759

30. Ruggeri M, Fortuna S, Rodeghiero F. Heterogeneity of terminology and clinical definitions in adult idiopathic thrombocytopenic purpura: a critical appraisal from a systematic review of the literature. *Haematologica*. 2008; 93(1) 98-103.

31. Donald M, Arnold, Kelton JG. Current Options for the Treatment of idiopathic thrombocytopenic purpura. *Semin Hematol*. 2007; 44(suppl 5):S12-S23

32. Ciurea SO, Hoffman R. Cytokines for the treatment of thrombocytopenia. *Semin Hematol*. 2007; 44:166-182.

33. Andersson J. Cytokines in idiopathic thrombocytopenic purpura (ITP). *Acta Pædiatr Suppl.* 1998; 424: 61-4.

34. Damodar S, Viswabandya A, George B, Mathews V, Chandy M, Srivastava A. Dapsone for chronic idiopathic thrombocytopenic purpura in children and adults – a report on 90 patients. *Eur J Haematol*. 2005: 75: 328-331

35. Cines DB, Bussel JB. How I treat idiopathic thrombocytopenic purpura (ITP). *Blood*. 2005;106:2244-2251.

36. Michel M. Immune thrombocytopenic purpura: epidemiology and implications for patients. *Eur J Haematol.* 2009; (Suppl. 71): 3-7.

37. Scaradavou A, Woo B, Woloski BMR, Rundles SC, Ettinger LJ, Aledort LM, Bussel JB. Intravenous Anti-D treatment of immune thrombocytopenic purpura: experience in 272 patients. *Blood*. 1997;89:2689-2700

38. Berchtold P, Mcmiiian R, Tani P, Nielsen SS, Blanchette VS. Autoantibodies against platelet membrane glycoproteins in children with acute and chronic immune thrombocytopenic purpura. *Blood.*1989; 74:1600- 1602

39. Stasi R, Evangelista ML, Stipa E, BuccisanoF, Venditti A, Amadori S. Idiopathic thrombocytopenic purpura: current concepts in pathophysiology and management. *Thromb Haemos*t. 2008; 99: 4–13

40. Schoonen WM, Kucera G, Coalson J, Li, L, Rutstein M, Mowat F, Fryzek J, Kaye JA. Epidemiology of immune thrombocytopenic purpura in the General Practice Research Database. *Br J Haematol.* 2009;145, 235–244

41. Michael D. Tarantino, George R, Buchanan. The pros and cons of drug therapy for immune thrombocytopenic purpura in children. *Hematol Oncol Clin N Am*. 2004; 18: 1301– 1314.

42. Provan D, Newland A, Norfolk D, Paula, Lilleyman J, Greer I, May A, Murphy M, Ouwehand W, Watson S. British Commitere for Satndards in Haematology, General Haematology Task Force. Guidelines for the investigation and

management of idiopathic thrombocytopenic purpura in adults, children and in pregnancy. *Br J Haematol*. 2003; 120: 574–596

43. Pizzuto J, Ambriz R. Therapeutic experience on 934 adults with idiopathic thrombocytopenic purpura: multicentric trial of the cooperative latin american group on hemostasis and thrombosis. ***Blood.***1984;64:1179-1183
44. Cheng Y, Wong RSM, Soo YOY, Chui CH, Lau FY, Chan NPH, Wong WS, Cheng G. Initial treatment of immune thrombocytopenic purpura with high-dose dexamethasone. *N Engl J Med*. 2003;349:831-6.
45. Stasi R, Poeta GD, Stipa E, Evangelista ML, Trawinska MM, Cooper N, Amadori S. Response to B-cell–depleting therapy with Rituximab reverts the abnormalities of T-cell subsets in patients with idiopathic thrombocytopenic purpura. ***Blood.*** 2007;110: 2924-2930
46. Parodi E, Rivetti E, Amendola G, Bisogno G, Calabrese R, Farruggia P, Giordano P, Matarese SMR, Nardi M, Nobili B, et al. Long-term follow-up analysis after Rituximab therapy in children with refractory symptomatic ITP: identification of factors predictive of a sustained response. *Br J Haematol*.2008;144: 552–558
47. Emilia G, Morselli M, Luppi M, Longo G, Marasca R, Gandini G, Ferrara L, D'Apollo N, Potenza L, Bertesi M, et al. Long-term salvage therapy with cyclosporine A in refractory idiopathic thrombocytopenic purpura. *Blood*.2002;99:1482-1485.
48. McMillan R. Immune-mediated thrombocytopenias: focus on chronic immune thrombocytopenic purpura. *Semin Haematol*.2007;44 (suppl 5):S1-S2
49. McMillan R. The Pathogenesis of Chronic Immune Thrombocytopenic Purpura. *Semin Hematol*. 2007;44(suppl 5):S3-S11

50. Stasi R, Provan D. Management of Immune Thrombocytopenic Purpura in Adults. *Mayo Clin Proc*. 2004;79:504-522

51. George JN. Management of patients with refractory immune thrombocytopenic purpura. *J Thromb Haemost*. 2006; 4: 1664-72.

52. Portielje JEA, Westendorp RGJ, Nelemans HCK, Brand A. Morbidity and mortality in adults with idiopathic thrombocytopenic purpura. *Blood*. 2001;97:2549-2554

53. Boruchov DM, Gururangan S, Driscoll MC, Bussel JB. Multiagent induction and maintenance therapy for patients with refractory immune thrombocytopenic purpura (ITP). *Blood*. 2007;110:3526-3531

54. Panzer S. New therapeutic options for adult chronic immune thrombocytopenic purpura: a brief review. *Vox Sanguinis*.2008;94:1–5

55. Glanz J, France E, Xu S, Hayes T, Hambidge. A population-based, multisite cohort study of the predictors of chronic idiopathic thrombocytopenic purpura in children. *Paediatrics.* 2008;121:506-512

56. Warner M, Wasi P, Couban S, Hayward C, Warkentin T, Kelton JG. Failure of pulse high-dose dexamethasone in chronic idiopathic immune thrombocytopenia. Am J Hematol. 1997;54:267–270

57. Tarantino M. Recent advances in the treatment of childhood immune thrombocytopenic purpura. *Semin Hematol*.2006;43 (Suppl 5):S11-S17

58. Psaila B, Bussel JB. Refractory immune thrombocytopenic purpura: current strategies for investigation and management. *Br J Haematol*. 2008; 143: 16–26

59. Bussel JB, Tarantino M. Review of therapies for immune thrombocytopenic purpura. *Semin Hematol*. 2006;43(Suppl 5):S1-S2.

60. Chavez JG, Cruz AM, Cervantes LM, Esparza MGR, Ojeda JV. Rituximab therapy for chonic and refractory immune thrombocytopenic purpura: a long-term follow-up analysis. *Ann Hematol*.2007; 86:871–877

61. Arnold DM, Dentali F, Crowther MA, Meyer RM, Cook RJ, Sigouin C, Fraser GA, Lim W, Kelton JG. Systematic review: efficacy and safety of Rituximab for adults with idiopathic thrombocytopenic purpura. *Ann Intern Med.*2007;146:25-33.

62. Newland A.Thrombopoietin mimetic agents in the management of immune thrombocytopenic purpura. *Semin Hematol*. 2007;44(Suppl 5):S35-S45

63. Hayes MM, Jacobs P, Wood L, Dent DM. Splenic pathology in immune thrombocytopenia. *J Clin Pathol*. 1985;38:985-988

64. Bussel J. Treatment of immune thrombocytopenic purpura in adults. *Semin Hematol*. 2006;43(suppl 5):S3-S10

65. The American Society of Hematology ITP Practice Guideline Panel. Diagnosis and Treatment of Idiopathic Thrombocytopenic Purpura: Recommendations of the American Society of Hematology. *Ann Intern Med*.1997;126:319-326

66. Bussel JB, Cheng G, Saleh MN, Psaila B, Kovaleva L, Meddeb B, Kloczko J,, Hassani H, Mayer B, Stone NL, et al. Eltrombopag for the treatment of chronic idiopathic thrombocytopenic purpura. *N Engl J Med*. 2007; 357:2237-47.

67. Gaiger A, Neumeister A, Heinzl H, Pabinger I, Panzer S. HLA class-I and -Il antigens in chronic idiopathic autoimmune thrombocytopenia. *Ann Hematol*. 1994; 68:299-302

68. Hézard N, Simon G, Macé C, Jallu V, Kaplan C, Nguyen P. Is flow cytometry accurate enough to screen platelet autoantibodies? Transfusion.2008;48:513-518.

69. Aster RH. Iimmune thrombocytopenia caused by glycoprotein IIb/IIIa inhibitors. *Chest.*2005; 127:53S–59S

70. Jubelirer SJ, Harpold R. The role of the bone marrow examination in the diagnosis of immune thrombocytopenic purpura: case series and literature review. Clin Appl Thromb Hemost. 2002;8(1):73-76

71. Neanaey WAE, Barakat SS, Ahmed MAR, Nabie WMHE, Ahmed MES. The relation between HLA-DRB1 alleles and the outcome of therapy in children with idiopathic thrombocytopenic purpura. *Egypt J Immunol.* 2005;12:29-38

72. Kuwana M, Kaburaki J, Pandey J P, Murata M, Kawakami Y, Inoko H, Ikeda Y. HLA class II alleles in Japanese patients with immune thrombocytopenic purpura. Associations with anti-platelet glycoprotein autoantibodies and responses to splenectomy. Tissue Antigens. 2000;56(4):337-343**.**

73. Freedman J, Blanchette M. Idiopathic thrombocytopenic purpura (ITP): a historical odyssey. *Acta Pædiatr Suppl.*1998;424:3-6.

74. Liebman HA. Immune thrombocytopenia (ITP): an historical perspective. *Hematology* 2008

75. Kuhne T, Buchanan GR, Zimmerman S, Michaels LA, Kohan R, Berchtold W, Imbach P. A prospective comparative study of 2540 infants and children with newly diagnosed idiopathic thrombocytopenic purpura (ITP) from the intercontinental childhood ITP study group. *J Pediatr*. 2003;143:605-8

76. Shojaiefard A, Mousavi S A, Faghihi S H, Abdollahzade S. Prediction of response to splenectomy in patients with idiopathic thrombocytopenic purpura. World J surg.2008;32:488-493.

77. Bourgeois E, Caulier M T, Delarozee C, Brouillard M, Bauters F, Fenaux P. Long –term follow up of chronic immune thrombocytopenic purpura refractory to splenectomy: a prospective analysis. *Br J Haematol.*003;120:1079-1088

78. Song S, Crow AR, Freedman J, Lazarus AH. Monoclonal IgG can ameliorate immune thrombocytopenia in a murine model of ITP: an alternative to IVIG. *Blood*.2003;101:3708-3713

79. Nugent D, McMillan R, Nichol JL, Slichter SJ. Pathogenesis of chronic immune thrombocytopenia: increased platelet destruction and/or decreased platelet production. *Br J Haematol*. 2009;1365-2141.

80. Nomura S, Matsuzaki T, Ozaki Y, Yamaoka M, Yoshimura C, Katsura K, Xie GL, Kagawa H, IshidaT, Fukuhara S. Clinical significance of hla-drb1*0410 in japanese patients with idiopathic thrombocytopenic purpura. *Blood.* 1998;91:3616-3622

81. George J N. Definition, diagnosis and treatment of immune thrombocytopenic purpura. *Haematologica*.2009; 94(6):759-762

82. Sakakura M, Wada H, Tawara I, Nobori T, SugiyamaT, Sagawa N, Shiku H. Reduced Cd4+Cd25+ T cells in patients with idiopathic thrombocytopenic purpura. *Thrombosis Research*.2007; 120: 187–193

83. Ahn YS, Horstman LL. Idiopathic thrombocytopenic purpura: pathophysiology and management. *Int J Hematol.* 2002;76 (Suppl II):123-131.

84. Choudhary DR, Kumar R, Saxena R, Mahapatra M, Kotwal A, Pati HP, Dixit A, Choudhry VP. Retrospective analysis of 1230 patients of immune thrombocytopenic purpura reporting to a tertiary care hospital in india from 1992–2004. *Blood* (ASH Annual Meeting Abstracts) 2004; 104:5294

85. Parray F. Q, Wani N. A, Wani K. A, Chowdri N. A, Wani R. A, Wani M. A. Splenectomy for immune thrombocytopenic purpura. *The Internet Journal of Surgery.* 2008;17(1)

86. 2nd Expert meeting 2006 on critical issues and future development of research in ITP. Yverdon-les-Bains, Switzerland, September 16-18, 2006. Pediatric Blood & Cancer 2006, Volume 47, pages 649-745

87. Fabris F, Tassan T, Ramon R, Carraro G, Randi ML, Luzzatto G, Moschino P, Girolami A. Age as the major predictive factor of long-term response to splenectomy in immune thrombocytopenic purpura. *Br J Haematol*. 2001;112: 637-640

88. Keidar A, Feldman M, Szold A. Analysis of outcome of laparoscopic splenectomy for idiopathic thrombocytopenic purpura by platelet count. *Am J Hematol.* 2005;80:95-100

89. Bourgeois E, Caulier MT, Delarozee C, Brouillard M, Bauters F, Fenaux P. Long-term follow-up of chronic autoimmune thrombocytopenic purpura refractory to splenectomy: a prospective analysis. *Br J Haematol*.2003;120: 1079-1088.

90. Rodeghiero F,Ruggeri M. Is splenectomy still the gold standard for the treatment of chronic ITP? *Am J Hematol*.2008;83:91.

91. Vianelli N, Galli M, de Vivo A, Intermesoli T, Giannini B, Mazzucconi MG, Barbui T, Tura S, Baccarani M. Efficacy and safety of splenectomy in immune thrombocytopenic purpura: long-term results of 402 cases. *Haematologica*.2005; 90:72-77.

MASTER CHART:

CODES :

Expansion of the abbreviations used in Column Headings (in the master chart):

DOD	Date of diagnosis	SHPR	Spleen Histopathology
DOS	Date of splenectomy	PerSCo	Perisplenectomy complications
Phase	Phase of ITP	AB	Antibiotics
AOD	Age at diagnosis	HS	Hospital stay
AOS	Age of splenectomy	IPoSR	Initial post splenectomy response
SAD	Symptom at diagnosis	DOIPoSR	Date of initial post splenectomy response
PAD	Platelet at diagnosis	PePC	Peak post splenectomy platelet count
DCT	Direct coomb's test	TtPePC	Time to peak post splenectomy platelet count
ANA	Antinuclear antibody	IPSoRDr	Initial post splenectomy response with drug
VM	Viral markers	PoSLOR	Post splenectomy loss of response
CM	Co-morbidities	DOPoSLOR	Date of post splenectomy loss of response
IT	Initial treatment	PoSR-2mo	Post splenectomy response at 2 months
RTIT	Response to initial treatment	TPoSLOR	Total post splenectomy loss of response
TPrSLOR	Total presplenectomy loss of response	OAT&R-Ref	Overall treatment & response of REF cases
SPrST	Subsequent presplenectomy treatment	DOLFU	Date of last follow up
PrSR	Presplenectomy response status	PLFU	Platelet count at last follow up
PerSS	Perisplenectomy symptoms	TLFU	Treatment at last follow up
DOV	Date of vaccination	D/A	Dead/Alive
PrSPC	Presplenectomy platelet count	Res/Ref	Type according to response to splenectomy-Responder/refractory
PerST	Perisplenectomy treatment	FR-LFU	Final response outcome as on last follow up
Ls/Lp	Laparoscopic/laparotomy splenectomy	OFUS	Over all follow up status
TOS	Type of splenectomy	Res-DOR	For responders, date since when in response
PRC	PRC transfusion	Ref-DOR	For ref ITP in response, date since when in last response
Spln	Splenunculi	DODe	Date of death

PHASE OF ITP	
1	PERSISTENT
2	CHRONIC
VIRAL MARKERS	
0	NA
1	Hepatitis C positive
2	Hepatitis B positive
3	Negative
AUTO – IMMUNE MARKERS	
0	NA
1	POSITIVE

SYMPTOMS AT DIAGNOSIS; PERI SPLENECTOMY SYMPTOMS	
0	NA
1	Skin only
2	Mucosal only
3	Skin+ /Mucosal + Other
4	Menorrhagia ± Other Bleeds
5	ICH+/Other Bleed
6	Asymptomatic

CO-MORBIDITIES	
0	NA
1	Thyroid Disease-Hypothyroidism
2	Hypertension/IHD
3	Diabetes Mellitus
4	H/O Tuberculosis/Hansen's Disease
5	Others
6	Nil

RESPONSE TO INTIAL TREATMENT	
0	NA
1	R (Response)
2	CR (Complete Response)
3	NR (No Response)

PLATELET COUNT AT DIAGNOSIS PRE-SPLENECTOMY PLATELET COUNT	
0	**NA**
1	Patients with platelet count $\leq 10 \times 10^9$/L
2	Patients with platelet count 11-30 x 10^9/L
3	Patients with Platelet count 31-100 x 10^9/L
4	Patients with platelet count > 100 x 10^9/L

INITIAL TREATMENT (DRUG)	
0	NA
1	STEROIDS (pred,dexa,M.pred)
2	IVIG +/pred
3	ANTI-D/pred
4	Others (pred+vincristine)

SUBSEQUENT PRESPLENECTOMY TREATMENT REGIMENS	
0	NA
1	Pred,M.pred, HC,Dexa
2	Dapsone ± steroid
3	Danazol ±steroid
4	Azathioprine ± steroid
5	Cyclophosphamide /vincristine ± steroid
6	Cyclosporine/MMF ± steroid
7	Dapsone + Azoran ± steroid
8	Dapsone±Azoran + Danazol ± Steroid
9	Other combination chemotherapy ± anti-D/IVIG
10	Others (Homeo/Siddha/Ayurveda)
11	No treatment

TYPE OF SPLENECTOMY	
1	Laparotomy
2	Laparoscopic
1	Elective
2	Emergency
PRE SPLENECTOMY RESPONSE STATUS	
0	NA
1	SD (Steroid dependent)
2	SR (Not Responding To Steroid)
3	Not Responding To Multiple Agents (Steroid/Dapsone/Azoran)

PERI SPLENECTOMY TREATMENT	
0	NA
1	HDD
2	PRED
3	HC (Hydrocortisone)
4	IVIG ± steroid
5	No Treatment

PRC TRANSFUSION	
0	**NA**
1	**yes**
2	**no**

SPLENECULI	
0	NA
1	YES
2	NIL
SPLEEN HPR	
0	NA
1	Congestion
2	Follicular Hyperplasia
3	Tuberculosis
4	Hyaline Arteriolar Sclerosis

PERI SPLENECTOMY COMPLICATIONS	
0	**NA**
1	Hemorrhage
2	Infection
3	Death
4	DVT/PE
5	NIL
ANTIBIOTIC REQUIREMENT	
0	NA
1	YES
2	NO

INITIAL POST SPLENECTOMY RESPONSE (CR/R/NR) - POST SPLENECTOMY RESPONSE AT 2 MONTHS	
0	Not applicable (NA)
1	R (Response)
2	CR (Complete response)
3 **3a**	LOCR (Loss of CR) LOCR and then responded
4 **4a**	LOR (Loss of Response) LOR and then responded
5	NR (No response)
6	LFU (Lost for follow up)
7	EXPIRED

-INITIAL POST SPLENECTOMY RESPONSE with/without DRUG -TREATMENT AT LAST FOLLOW UP	
0	not applicable (Cases with NR [No Response])
1	No Drug
2	On Steroid
3	On Dapsone± Steroid
4	On Danazol ± Steroid
5	On Azoran ± Steroid
6	On Combination Chemo
7	Others

POST SPLENECTOMY LOSS OF R1 (YES/NO)	
0	**NA (No Response/Lost for follow up)**
1	**yes**
2	**no**

POST SPLENECTOMY FOLLOW UP AT 2 MONTHS	
1	On follow up
2	Lost for follow up

Number of post splenectomy loss of R	
0	NA-NR/EXPIRED
1	**one**
2	**two**
3	**Three**
4	**four**
5	**five**
6	**nil**
7	**lost for follow up**

DEAD/ALIVE AS ON LAST Follow up	
1	Alive
2	Dead
TYPES OF ITP ACCORDING TO RESPONSE TO SPLENECTOMY	
0	NA (Expired immediate post splenectomy)
1	Responders (R/CR/LOCR)
2	Refractory ITP (NR/LOR)Responders (R/CR/LOCR)

FINAL OUTCOME AS ON LAST FOLLOW UP:		
1-5, 7,8,9: REFRACTORY CASES **1-5: REFRACTORY CASES (NR/LOR) WHO RESPONDED TO Rx & are in response**		
1	R1/CR1	
2	R2/CR2	
3	R3/CR3	
4	R4/CR4	
5	R5/CR5	
RESPONDERS: (Cases in R, CR and LOCR)		
6	**RESPONDRES with no subsequent loss of R1** (continuing in initial R1/CR1/LOCR1)	
7: REF ITP- CONTINUED IN (NR)		
7	7	SYMPTOMATIC
	7a	ASYMPTOMATIC
8: REF ITP IN LOSS OF R		
8	8	SYMPTOMATIC
	8a	ASYMPTOMATIC
9		NR went into spontaneous remission
10		EXPIRED

OVERALL FOLLOW UP STATUS	
1	**on follow up**
2	**lost to follow up**
3	**EXPIRED**
TREATMENT STATUS AS ON LAST FOLLOW UP	
0	NA (EXPIRED)
1	On treatment
2	Steroid dependent
3	Off treatment

OVERALL TREATMENT & RESPONSE OF REFRACTORY ITP	
Code	**Treatment + response status**
0	Group 0, responder
0a	Group 0, non-responder
1	Group 1, responder
1a	Group 1, non-responder
2	Group 2, responder
2a	Group 2, non-responder
3	Group 3, responder
3a	Group 3, non-responder
4	Group 4, responder
4a	Group 4, non-responder

MASTER CHART

Sl No	Sex	DOD	DOS	PHASE	AOD	AOS	SAD	PAD	DCT	ANA	VM	CM	IT	RTIT	TPrSLOR	SPrST	PrSR	PerSS	DOV	PrSPC	PerST	Ls/Lp	TOS	PRC
1	F	01.01.1985	03.14.1995	2	12	22	4	1	2	2	3	6	1	1	0	1	1	6	NA	1	5	1	1	1
2	F	01.01.1991	05.23.1995	2	12	16	0	0	0	0	0	0	1	2	0	0	0	0	NA	4	5	1	1	2
3	F	01.01.1993	06.20.1995	2	14	16	0	0	0	0	0	0	1	3	0	11	2	0	NA	2	5	1	1	0
4	F	02.14.1995	11.08.1995	1	26	26	4	0	2	2	3	6	1	3	0	11	2	4	NA	2	5	1	1	0
5	F	05.01.1995	11.13.1995	1	23	23	4	0	0	0	3	6	1	3	0	11	2	4	NA	3	5	1	1	1
6	M	09.03.1995	03.07.1996	1	23	23	1	2	2	0	3	6	1	3	0	11	2	6	02.20.1996	2	5	1	1	0
7	M	01.01.1989	03.26.1996	2	9	15	1	0	0	0	3	6	1	2	0	1	1	6	NA	3	5	1	1	2
8	F	04.01.1994	07.16.1996	2	24	26	4	0	0	0	3	5	1	1	1	1	1	4	NA	3	5	1	1	2
9	F	01.01.1996	12.01.1996	1	31	31	4	0	0	0	3	6	0	0	0	0	0	0	NA	0	0	1	1	0
10	F	04.01.1996	11.01.1996	1	22	22	4	0	0	0	3	6	1	3	0	11	2	4	NA	2	5	1	1	1
11	F	05.01.1996	12.03.1996	1	51	54	1	0	0	0	3	2	1	3	0	3	3	1	NA	2	5	1	1	1
12	F	05.15.1996	12.02.1996	1	29	30	1	2	2	2	3	6	1	1	0	1	2	1	NA	1	5	1	1	1
13	F	12.01.1995	03.12.1996	1	26	27	3	2	0	2	3	6	1	2	1	1	1	2	NA	2	0	1	1	1
14	F	06.01.1996	02.14.1997	1	28	24	1	1	0	0	3	6	1	1	0	1	2	6	NA	3	1	1	1	2
15	F	09.01.1996	05.26.1997	1	29	30	3	2	0	0	2	6	1	2	1	1	2	3	NA	2	2	1	1	1
16	F	03.01.1997	09.11.1997	1	33	35	3	0	0	0	3	6	1	3	0	1	1	3	NA	3	2	1	1	2
17	M	01.01.1996	01.28.1998	2	33	35	3	0	2	2	3	4	1	3	0	2	3	1	01.01.1998	1	5	1	1	1
18	F	11.01.1996	03.04.1998	2	27	29	4	1	2	2	3	6	1	2	1	1	1	4	NA	3	1	1	1	2
19	F	01.01.1997	03.31.1998	2	39	40	3	0	2	2	3	6	1	2	1	1	2	6	NA	3	1	1	1	1
20	F	08.24.1996	04.21.1998	2	18	20	4	0	1	1	3	6	1	2	3	1	1	6	12.19.1997	2	2	2	1	2
21	F	09.01.1997	05.05.1998	1	42	43	1	2	2	2	3	6	1	2	1	3	3	1	04.21.1998	1	0	1	1	1
22	M	11.01.1996	04.28.1998	2	46	48	1	1	2	1	3	2	1	2	1	1	1	6	01.01.1997	3	1	1	1	2
23	M	06.01.1997	04.22.1998	1	64	65	3	2	0	0	3	3	1	1	0	7	3	3	02.13.1998	2	5	1	1	2
24	F	04.27.1993	06.19.1998	2	13	17	4	3	0	0	3	5	1	2	2	1	1	4	05.18.1998	2	2	1	1	2
25	F	02.01.1998	12.22.1998	1	51	52	3	0	2	2	3	6	1	3	0	4	3	3	NA	3	2	1	1	2
26	F	01.01.1987	02.09.1998	2	8	19	4	1	2	2	3	5	1	1	0	1	2	4	01.09.1998	2	1	2	1	1
27	F	01.01.1998	01.08.1999	2	26	27	4	0	2	0	3	6	1	3	0	4	3	4	10.09.1998	2	0	1	1	1
28	F	06.01.1998	01.05.1999	1	22	22	3	1	2	2	3	5	1	3	0	1	2	2	NA	1	0	1	1	1
29	F	04.01.1998	02.10.1999	1	15	16	4	1	0	0	3	6	1	3	0	1	2	4	NA	1	0	1	1	1
30	F	02.01.1998	02.24.1999	2	22	23	4	1	2	2	3	6	1	2	1	1	1	4	01.15.1999	4	1	1	1	2
31	F	11.01.1998	06.09.1999	1	31	32	1	1	0	0	3	6	1	1	0	8	3	6	NA	1	0	1	1	0
32	F	11.01.1998	11.22.1999	2	38	39	4	1	2	2	3	6	1	3	0	2	3	1	11.17.1999	3	0	1	1	2
33	M	04.01.1999	11.17.1999	1	28	28	3	1	0	0	3	6	1	3	0	1	2	1	NA	2	5	1	1	1
34	M	06.09.1999	04.03.2000	1	9	15	3	1	0	0	3	6	1	3	1	2	1	6	02.01.2000	4	1	1	1	0
35	F	10.10.1997	09.05.2000	2	29	31	4	2	2	2	3	6	1	3	2	7	1	6	03.20.1998	3	2	1	1	2
36	F	11.01.1999	05.25.2000	1	22	23	4	2	0	0	3	6	1	1	0	1	2	4	NA	2	2	1	1	1
37	M	01.01.1994	07.17.2000	2	9	15	3	0	0	2	3	6	1	1	1	2	3	2	04.06.1999	2	0	1	1	0
38	F	01.01.1994	09.25.2000	2	22	28	3	0	0	0	3	1	1	2	1	2	1	4	08.08.2000	2	2	1	1	0
39	F	11.01.1999	10.25.2000	1	27	28	4	3	2	2	3	6	1	1	1	7	1	6	03.24.2000	4	1	1	1	2
40	F	04.01.2000	10.16.2000	1	28	28	3	1	2	2	3	6	1	3	0	4	3	4	09.28.2000	1	1	1	1	1
41	F	03.15.2000	11.03.2000	1	29	30	4	1	2	2	3	6	1	1	0	2	1	6	06.28.2000	4	5	2	1	2
42	F	05.01.2000	08.07.2000	1	34	34	3	0	2	2	3	6	2	1	0	11	2	6	NA	3	1	1	1	2
43	F	04.01.2000	01.08.2001	1	23	24	4	1	2	2	3	6	1	3	0	2	3	4	NA	1	1	1	1	1
44	F	04.24.2000	01.25.2001	1	15	16	3	1	0	2	3	6	1	2	1	2	1	6	12.08.2000	4	2	1	1	2
45	F	07.01.2000	02.05.2001	1	21	22	1	1	2	2	3	6	1	3	0	1	2	1	NA	3	1	1	1	2
46	F	12.01.1999	02.14.2001	2	21	23	4	1	0	0	3	6	1	3	0	4	3	4	11.07.2000	3	2	1	1	2
47	F	12.01.1995	11.07.2001	2	57	61	3	1	0	0	3	2	1	2	3	7	1	3	08.05.1997	1	4	1	2	1
48	F	01.01.1995	05.23.2001	2	55	61	1	1	2	1	3	2	1	2	1	1	1	6	NA	4	2	1	2	2
49	M	01.01.1996	10.08.2001	2	12	17	3	1	0	0	3	6	1	1	0	1	1	3	NA	4	1	1	1	2
50	F	06.01.2000	11.19.2001	2	35	36	4	1	1	0	0	5	1	2	1	2	1	4	04.20.2001	3	1	1	1	1
51	F	01.01.1999	07.12.2001	2	31	31	1	2	0	2	3	6	1	1	1	4	1	6	02.22.1999	1	1	1	1	1
52	F	10.01.2001	04.29.2002	1	29	29	4	1	2	2	3	6	1	3	0	2	3	4	04.01.2002	2	1	1	1	1
53	F	02.01.2001	05.13.2002	2	16	17	4	2	2	2	2	6	1	2	2	2	3	4	05.29.2001	3	1	1	1	2
54	F	03.01.2002	09.09.2002	1	17	17	1	0	0	0	3	6	1	3	0	7	3	6	08.27.2002	3	1	1	1	2
55	F	02.01.2002	09.30.2002	1	25	25	5	1	1	2	3	6	1	3	0	9	3	5	09.27.2002	1	1	1	2	1
56	F	08.01.1999	08.12.2002	2	17	20	1	2	1	1	3	6	1	2	1	1	2	6	07.26.2002	4	1	1	1	2
57	M	06.14.2000	03.17.2003	2	18	21	2	1	0	0	3	6	1	3	0	7	3	6	09.01.2002	3	1	1	1	1
58	F	07.01.2002	06.23.2003	1	44	45	4	1	2	2	3	3	1	3	0	7	3	4	09.01.2002	4	1	1	1	2
59	F	12.26.2002	06.30.2003	1	49	50	4	3	2	2	3	3	1	3	0	7	3	2	02.19.2003	2	1	1	1	1
60	F	07.27.1995	07.02.2003	2	9	17	4	1	0	0	3	6	1	3	0	7	3	2	05.16.2003	1	1	1	1	1
61	M	09.06.2002	07.28.2003	1	53	54	3	1	2	1	3	4	1	1	0	7	3	6	07.21.2003	2	1	1	1	1
62	F	08.13.1999	09.10.2003	2	51	55	4	2	2	2	3	2	1	3	1	7	1	6	08.05.2003	3	2	1	1	2
63	M	04.01.2003	10.27.2003	1	33	33	1	0	0	2	3	6	1	3	0	4	3	6	10.21.2003	3	1	1	1	2
64	F	01.01.2000	11.10.2003	2	25	28	4	3	2	1	3	6	1	1	0	7	1	4	09.22.2003	1	1	1	1	1
65	F	04.01.2003	11.17.2003	1	22	22	3	1	0	2	3	6	1	1	0	7	1	4	10.15.2003	4	1	1	1	2
66	M	01.11.2000	07.07.2003	2	24	27	3	2	2	2	3	6	1	3	0	7	3	6	05.23.2003	3	1	1	1	2
67	M	05.01.2002	12.22.2003	2	18	19	3	2	0	0	3	6	1	1	0	1	1	3	07.09.2002	2	2	1	1	1
68	M	04.01.2003	07.28.2003	1	38	38	3	1	2	0	3	6	1	2	1	1	2	3	07.23.2003	1	1	1	2	1
69	F	04.09.2003	01.28.2004	1	21	22	4	1	1	2	3	6	1	3	0	2	3	4	01.27.2004	1	5	1	1	1
70	F	08.28.2003	05.20.2004	1	45	46	1	1	2	2	3	1	1	1	0	7	3	5	05.07.2004	2	1	1	2	1

71	F	09.04.2001	06.14.2004	2	23	26	4	1	2	1	3	6	1	2	4	4	1	6	06.01.2004	3	1	1	1	2
72	F	01.01.2004	06.21.2004	1	21	22	4	2	0	1	3	6	1	3	0	2	1	6	05.25.2004	4	1	1	1	2
73	F	01.01.2004	08.12.2004	1	57	57	1	2	1	1	3	5	1	1	0	1	1	6	08.11.2004	3	1	1	1	2
74	F	01.01.1993	10.06.2004	2	5	16	3	3	2	2	0	6	1	2	4	1	2	4	10.10.2003	2	1	1	1	2
75	M	11.01.2003	02.25.2004	1	51	52	3	1	2	2	3	3	2	3	0	4	3	3	02.16.2004	1	2	1	1	1
76	F	09.01.2003	02.16.2005	2	16	18	4	0	0	2	3	6	1	1	0	7	3	4	02.11.2005	1	5	1	1	1
77	F	05.29.2003	02.23.2005	2	20	22	4	1	0	2	3	6	1	3	0	7	3	4	11.28.2003	1	5	1	1	2
78	F	12.26.2003	02.28.2005	2	42	44	4	1	0	2	3	6	1	3	0	9	3	4	02.08.2005	3	1	1	1	1
79	F	01.01.2000	03.02.2005	2	15	20	4	2	2	2	3	1	1	1	0	1	1	4	02.23.2005	1	1	1	1	1
80	F	04.01.2004	03.14.2005	1	29	30	4	2	1	1	3	6	1	3	1	4	3	6	09.01.2004	4	1	1	1	2
81	M	08.01.2004	07.13.2005	1	14	15	1	1	2	0	3	6	1	3	0	7	3	1	02.09.2005	1	5	1	1	2
82	F	03.04.2005	11.16.2005	1	40	41	4	1	1	0	3	5	1	3	1	8	3	5	10.05.2005	1	1	2	2	1
83	F	07.01.1999	03.16.2005	2	13	18	4	0	2	0	3	6	1	1	0	7	1	4	02.23.2005	2	5	1	1	2
84	F	11.01.2003	09.21.2005	2	18	20	5	2	0	1	3	6	1	1	1	7	3	4	07.23.2005	1	5	1	1	1
85	F	03.01.2000	06.01.2005	2	28	33	1	1	2	2	3	5	1	1	0	2	3	4	05.31.2005	4	1	1	1	2
86	F	02.01.2005	05.29.2006	2	39	40	4	2	0	0	3	5	1	3	0	4	3	4	05.26.2006	2	1	1	1	1
87	F	04.01.2006	09.27.2006	1	20	20	3	2	1	1	3	6	1	3	0	9	3	2	09.15.2006	1	1	1	1	2
88	M	05.13.2004	07.24.2006	2	13	15	3	2	0	0	3	6	2	3	2	7	1	6	08.06.2005	3	1	1	1	2
89	F	04.18.2005	08.02.2006	2	14	15	4	3	2	2	3	6	1	2	2	2	1	1	07.21.2006	1	1	1	1	1
90	F	12.01.2005	03.27.2006	1	15	16	5	1	2	1	3	6	1	1	0	4	3	6	03.17.2006	4	1	1	1	2
91	F	11.01.2005	02.08.2006	1	58	58	2	1	2	2	3	2	1	2	1	8	1	5	02.08.2006	1	1	1	2	1
92	F	06.08.2004	06.06.2007	2	18	20	5	1	2	1	3	6	1	1	2	7	1	4	05.15.2007	4	1	1	1	2
93	M	06.14.2005	03.26.2007	2	20	22	3	2	2	0	3	5	1	2	4	7	1	6	03.21.2007	3	1	1	1	1
94	M	03.25.2006	04.02.2007	2	25	26	1	2	2	2	3	6	1	1	0	4	3	6	02.07.2007	1	5	1	1	2
95	M	04.15.2006	04.09.2007	2	41	42	6	3	1	2	3	3	1	1	0	7	3	6	03.31.2007	1	1	1	1	1
96	F	01.01.1999	04.16.2007	2	9	17	3	1	2	2	3	6	1	2	2	7	1	4	04.29.2005	3	1	1	1	2
97	F	01.01.2001	07.30.2007	2	22	28	4	0	2	1	3	6	1	2	2	7	1	4	10.28.2003	3	1	1	1	2
98	M	08.01.2006	10.31.2007	2	32	33	3	1	1	1	3	2	2	3	0	7	3	6	08.17.2007	2	1	1	1	1
99	F	09.28.2006	08.06.2007	1	17	18	4	1	2	1	3	6	1	2	1	4	1	4	07.30.2007	4	1	1	1	2
100	F	02.01.2007	11.02.2007	1	21	21	4	0	2	2	3	6	1	3	0	2	3	4	10.06.2007	3	1	2	1	2
101	F	02.01.2004	08.06.2007	2	15	18	3	0	0	0	3	6	1	1	1	7	3	6	04.16.2007	1	1	1	1	1
102	F	12.01.2006	06.06.2007	1	21	21	4	2	2	1	3	1	1	1	0	4	1	6	05.23.2007	4	1	1	1	2
103	F	01.01.1997	01.07.2008	2	24	34	4	1	2	2	3	3	1	1	3	8	1	4	12.28.2007	4	1	1	1	2
104	F	05.06.2000	12.26.2007	2	17	22	4	2	1	1	3	6	1	2	3	7	1	5	12.12.2007	2	1	1	2	2
105	F	07.20.2005	01.15.2008	2	25	27	4	2	2	2	3	6	1	2	3	7	1	4	12.22.2007	2	1	2	1	1
106	F	11.01.2005	02.18.2008	2	13	16	4	1	2	2	3	6	1	1	0	2	1	4	01.29.2008	2	1	1	1	2
107	M	03.01.2006	03.11.2008	2	36	38	3	2	2	0	3	6	1	1	2	2	1	6	02.20.2007	2	5	1	1	1
108	M	10.13.1984	07.30.2008	2	15	29	1	0	2	0	3	6	1	2	2	5	1	1	05.10.2008	3	1	1	1	2
109	F	02.01.2008	08.13.2008	1	31	31	3	1	2	2	3	6	1	1	0	9	1	3	07.29.2008	3	1	1	1	1
110	F	01.01.2007	04.15.2008	2	36	37	3	1	0	2	3	6	1	3	0	8	3	6	03.17.2008	2	5	2	1	1
111	F	04.01.2004	02.19.2008	2	15	19	1	2	0	0	3	6	1	0	1	7	3	4	01.15.2008	1	1	1	1	1
112	F	04.14.2003	05.09.2008	2	14	19	1	2	2	2	3	6	1	1	1	7	1	1	04.18.2008	4	2	2	1	2
113	F	08.20.2005	05.22.2008	2	34	37	6	2	2	2	3	1	1	1	1	2	3	6	01.01.2008	4	2	2	1	2
114	F	04.01.2006	06.17.2008	2	39	41	4	1	2	2	3	6	1	2	1	9	3	6	01.25.2008	1	2	2	1	2
115	F	12.20.2007	01.11.2008	1	24	25	4	1	1	2	3	6	4	3	0	11	2	4	01.11.2008	1	1	1	2	1
116	F	07.01.2008	02.25.2009	1	19	20	4	1	2	1	3	1	3	3	0	9	1	5	09.06.2008	3	1	1	1	2
117	F	07.01.2008	02.17.2009	1	24	25	5	2	2	2	3	6	1	3	0	1	2	5	02.13.2009	1	1	1	2	1
118	M	05.01.2008	06.22.2009	2	27	28	3	1	1	1	3	6	2	3	1	8	3	3	09.04.2008	3	1	1	1	2
119	F	11.24.2007	07.17.2009	2	35	37	4	2	1	2	3	6	1	1	0	7	3	4	06.03.2009	3	1	2	1	2
120	F	10.07.1994	06.06.1995	1	16	17	4	0	2	2	3	4	1	3	0	11	2	4	10.18.1994	1	5	1	1	0
121	F	01.01.1995	08.04.1995	1	38	38	4	1	2	2	3	6	1	3	0	1	2	4	NA	1	5	1	1	2
122	F	11.08.1994	11.28.1995	2	16	17	4	1	2	2	3	6	1	3	0	5	3	4	NOT GIVEN	1	5	1	1	1
123	F	03.01.1996	10.23.1996	1	32	32	2	1	2	2	3	5	1	3	0	3	3	5	09.24.1996	3	5	1	2	1
124	F	05.25.1996	12.05.1996	1	22	22	4	1	2	2	3	6	1	1	1	1	1	4	10.25.1996	3	2	1	1	2
125	F	01.01.1996	01.03.1997	2	31	32	1	2	2	2	3	6	1	3	0	1	1	6	11.09.1996	2	1	1	1	0
126	F	01.01.1997	06.17.1997	1	40	40	5	1	0	2	3	6	1	1	NA	1	2	5	NA	2	0	1	1	1
127	F	08.20.1997	02.03.1998	1	14	15	4	1	2	0	3	6	1	3	1	7	3	4	12.17.1997	1	5	2	1	0
128	M	02.01.1998	11.20.1998	1	19	19	3	1	0	0	0	5	1	2	1	2	3	3	NA	2	5	1	1	1
129	F	03.9.1997	01.07.1999	2	21	23	4	2	1	1	3	6	1	2	1	1	2	2	12.11.1998	1	1	1	1	1
130	M	02.11.1998	01.22.1999	1	59	58	1	2	0	0	3	2	1	1	0	7	3	6	07.10.1998	0	0	1	1	0
131	F	01.12.1999	07.14.1999	1	33	33	3	1	2	2	3	5	1	1	0	2	3	3	06.08.1999	4	1	1	1	2
132	F	01.01.1998	07.05.1999	2	34	35	4	1	0	0	3	6	1	1	0	2	3	4	NA	1	0	1	1	0
133	F	03.01.1998	11.22.1999	2	18	19	4	1	2	2	3	5	1	3	1	2	3	4	10.31.1999	1	1	1	1	0
134	M	10.01.1999	05.08.2000	1	52	53	3	3	0	0	3	6	1	3	0	4	3	2	04.08.2000	1	1	1	1	0
135	M	01.01.1996	06.26.2000	2	13	17	3	1	0	0	3	6	1	3	0	9	3	5	06.09.2000	2	1	1	2	1
136	M	09.01.1999	09.04.2000	2	24	25	3	2	0	0	3	4	1	2	1	1	2	6	08.10.2000	1	0	1	1	1
137	M	06.01.2000	01.15.2001	1	17	18	3	1	0	0	3	6	1	3	0	2	3	3	10.03.2000	3	1	1	1	1
138	M	09.01.2000	02.13.2002	2	12	16	3	0	0	0	3	6	1	2	1	2	1	6	01.10.2002	4	1	1	1	2
139	F	10.01.2001	04.15.2002	1	53	54	3	1	0	2	3	3	1	3	0	4	3	6	12.01.2001	1	1	1	1	2
140	F	01.01.1993	04.15.2002	2	52	61	3	2	0	0	3	1	1	2	1	9	3	1	04.06.1999	1	1	1	1	1
141	F	05.27.1999	07.08.2002	2	47	50	1	3	2	2	3	5	1	1	3	2	3	6	06.02.1999	2	0	1	1	1
142	F	01.01.2000	03.03.2003	2	19	22	4	2	2	2	3	6	1	3	0	9	3	4	02.05.2003	3	1	1	1	2
143	M	10.01.2001	03.31.2003	2	60	61	1	2	2	2	3	3	1	1	0	7	1	6	03.25.2003	3	1	1	1	2
144	M	12.01.2000	01.05.2004	2	23	27	3	2	0	0	3	6	1	1	0	9	3	6	05.11.2001	1	1	1	1	1

145	M	04.14.1997	07.23.2004	2	57	59	3	2	0	0	3	1	1	1	0	9	3	6	07.21.2004	3	5	1	2	1
146	F	06.09.2003	08.24.2004	2	26	27	3	1	1	0	3	5	1	1	2	7	1	3	07.23.2004	1	1	1	2	1
147	M	01.01.2004	07.12.2004	1	40	40	3	1	2	2	3	3	1	1	0	2	3	6	06.08.2004	1	5	1	1	1
148	F	02.01.2004	09.22.2004	1	16	16	4	2	2	2	3	6	1	1	0	7	3	2	04.30.2004	2	1	1	1	1
149	F	01.01.1991	09.29.2004	2	34	47	3	1	0	0	3	6	1	2	4	9	1	2	09.24.2004	1	1	1	1	1
150	F	09.01.2004	03.08.2005	1	21	22	4	2	2	0	3	6	2	3	0	4	3	4	01.11.2004	1	1	1	1	1
151	F	04.01.2004	03.11.2005	1	29	30	4	2	2	1	3	6	1	3	0	3	3	4	NA	0	0	1	1	2
152	M	01.01.2003	04.10.2006	2	47	50	2	1	2	2	3	3	1	1	0	7	3	6	10.08.2004	3	1	1	1	2
153	F	04.01.2006	10.25.2006	1	35	35	4	2	2	2	3	6	2	3	0	2	3	4	10-16-2006	1	1	1	1	1
154	F	03.01.2001	02.20.2006	2	52	57	1	1	0	0	3	1	1	1	1	8	1	6	02.14.2006	1	5	1	1	1
155	F	06.26.2005	12.12.2007	2	17	19	4	1	2	0	3	1	1	1	2	2	1	4	11.27.2007	3	1	1	1	2
156	F	01.01.2006	05.03.2007	2	27	27	4	1	1	2	3	6	1	1	0	9	1	4	04.19.2007	0	0	1	1	1
157	F	10.15.2004	10.18.2007	2	24	27	1	2	2	2	3	6	1	1	1	2	1	6	10.18.2007	1	1	1	2	1
158	M	11.04.2004	03.24.2008	2	21	24	2	0	0	2	3	6	1	1	1	7	3	6	NA	3	1	1	1	1
159	M	01.01.1998	08.25.2008	2	39	48	3	1	1	2	3	5	1	2	1	1	2	6	08.18.2008	1	4	1	2	2
160	M	03.01.2005	04.23.2008	2	37	40	3	1	0	0	3	2	1	3	0	7	3	6	02.22.2008	3	4	1	1	2
161	M	12-01.2006	06-30-2008	2	48	50	1	2	2	1	3	4	1	3	1	9	3	6	05.02.2008	1	1	1	1	2
162	M	01.01.2008	08.20.2008	1	58	58	3	1	2	2	3	6	1	3	0	8	3	2	08.06.2008	1	1	1	1	1
163	F	04.04.2007	01.22.2008	1	32	33	3	0	2	2	3	5	1	1	1	9	1	6	12.04.2007	4	1	2	1	1
164	M	05.01.2007	02.26.2008	1	17	18	3	0	2	2	3	6	1	3	1	2	3	1	02.09.2008	1	1	2	1	1
165	F	01.01.1998	05.16.2008	2	22	32	4	0	2	2	3	1	1	2	2	2	1	1	03.14.2008	1	5	2	1	1
166	F	01.01.2000	01.06.2009	2	12	21	4	3	1	2	3	6	1	3	0	4	3	6	11.25.2008	1	1	2	1	1
167	M	11.01.2007	07.20.2009	2	17	20	3	2	2	2	3	5	1	2	1	7	3	2	03.13.2009	2	5	1	1	1
168	F	11.01.1994	02.16.1995	1	9	10	3	2	0	0	3	6	1	3		1	2	6	01.21.1995	2	5	1	1	1
169	M	01.01.1994	04.11.1995	2	10	11	3	0	0	0	3	6	1	3		1	2	3	02.24.1995	1	5	1	1	1
170	F	01.01.1990	04.11.1995	2	9	14	0	0	0	0	0	0	1	2		1	1	0	NA	4	5	1	1	2
171	F	01.01.1995	06.29.1995	1	6	6	1	0	0	0	0	0	1	2		0	1	6	NA	2	5	1	1	1
172	F	12.01.1994	10.10.1995	1	10	11	1	0	0	0	3	6	1	2		1	1	6	NA	4	5	1	1	2
173	F	12.01.1994	10.17.1995	1	11	12	3	2	2	1	3	5	1	2	1	1	2	3	09.26.1995	2	5	1	1	0
174	F	01.01.1986	08.12.1995	2	5	14	1	0	0	0	3	6	1	2		1	1	6	NA	4	5	1	1	2
175	M	01.01.1994	03.12.1996	2	7	9	3	1	0	0	3	6	1	2		1	1	6	NA	4	0	1	1	2
176	M	10.05.1995	04.09.1996	1	9	9	1	2	0	0	3	6	1	1		1	1	6	NA	2	5	1	1	1
177	F	01.01.1996	10.09.1996	1	5	6	1	0	0	0	3	6	1	3		0	2	6	NA	1	1	1	1	1
178	M	02.06.1996	09.19.1996	1	7	7	1	0	0	0	3	6	1	3		0	2	0	NA	1	1	1	1	1
179	F	01.01.1988	02.07.1997	2	5	14	3	1	0	0	3	6	1	3		1	2	2	NA	1	1	1	1	1
180	M	12.01.1993	03.11.1997	2	7	11	3	2	0	0	3	6	1	3		1	2	1	03.01.1997	4	2	1	1	2
181	M	06.01.1996	04.08.1997	1	8	9	3	1	0	0	3	6	1	1		1	1	3	03.21.1997	3	3	1	1	1
182	M	11.01.1996	05.27.1997	1	6	7	3	0	0	0	3	6	1	3		11	2	3	05.09.1997	0	0	1	1	1
183	F	05.01.1995	05.23.1997	2	12	14	4	1	2	0	3	6	1	2	1	1	2	3	04.02.1997	2	0	1	1	1
184	F	01.01.1990	06.10.1997	2	4	11	3	0	0	0	3	6	1	2	1	1	2	3	05.24.1997	2	0	1	1	2
185	M	04.01.1994	02.17.1998	2	4	8	1	2	0	0	3	6	1	3		9	3	1	NA	2	0	1	1	1
186	M	01.01.1995	05.26.1998	2	4	7	1	2	0	0	3	6	1	2	1	1	2	6	05.05.1998	4	0	1	1	2
187	M	04.01.1998	07.09.1998	1	9	9	3	0	0	0	3	6	1	2	1	1	1	3	06.23.1998	3	1	1	1	1
188	M	07.01.1998	10.02.1998	1	14	14	2	1	2	2	3	6	1	3		4	3	5	09.30.1998	1	1	1	2	1
189	F	04.02.1998	07.01.1999	2	7	8	3	1	0	0	3	6	1	1		2	3	3	05.20.1999	1	5	1	1	2
190	M	01.19.1998	12.06.1999	2	13	14	3	2	0	0	3	6	1	1		2	3	3	01.19.1999	3	1	1	1	2
191	F	01.01.1999	11.08.1999	1	13	13	4	0	2	2	3	6	1	3		2	3	4	09.01.1999	3	0	1	1	2
192	M	01.01.1998	01.20.2000	2	3	5	1	1	0	0	3	6	2	3		8	3	1	09.01.1999	1	1	1	1	1
193	M	05.01.1999	01.30.2000	1	12	13	1	1	0	0	3	6	1	1		1	2	1	NA	1	0	1	1	0
194	M	05.11.1999	04.24.2000	1	13	14	1	1	0	0	3	6	1	3		2	3	6	12.28.1999	1	1	2	1	1
195	M	01.01.1999	04.06.2000	2	11	12	1	2	0	0	3	6	1	2	1	1	3	6	03.15.2000	2	2	1	1	1
196	M	10.01.1999	10.19.2000	2	10	11	3	1	0	0	3	6	1	1		2	1	6	09.20.2000	4	1	1	1	0
197	M	04.01.2000	11.30.2000	1	6	7	1	0	0	0	3	6	1	3		4	3	6	NA	3	1	1	1	2
198	F	07.01.2000	03.07.2001	1	11	12	4	1	2	0	3	6	1	3		4	3	4	NA	2	1	1	1	1
199	M	05.01.2000	05.21.2001	2	10	11	1	1	0	0	3	5	1	3		1	2	6	NA	1	1	1	1	1
200	M	10.01.2001	04.19.2002	1	10	11	1	0	0	0	3	6	1	1		1	1	6	NA	3	0	1	1	2
201	F	09.01.1999	04.24.2002	2	4	7	1	0	0	0		6	1	2	3	2	1	1	10.01.2000	2	2	1	1	1
202	F	01.01.2003	08.25.2003	1	9	10	1	2	2	2	3	6	1	3		7	3	1	07.11.2003	3	1	1	1	2
203	F	01.01.2003	11.17.2003	1	9	9	3	3	1	2	3	6	2	2	1	9	3	3	08.01.2003	2	1	1	1	1
204	F	01.01.2001	01.16.2004	2	6	9	1	2	2	2	3	6	1	3		2	3	6	01.02.2004	1	5	1	1	1
205	F	02.05.2003	06.03.2004	2	13	14	6	2	0	0	1	5	1	3		2	1	2	06.02.2004	3	1	1	1	2
206	M	10.18.2003	07.28.2004	1	11	12	3	1	2	2	3	6	1	3		7	3	6	06.15.2004	2	1	1	1	0
207	M	01.01.2003	01.16.2004	2	3	4	3	1	2	2	3	5	1	3		4	3	3	12.27.2003	2	1	1	1	1
208	F	08.10.2004	06.09.2005	1	9	10	1	1	0	1	3	6	1	3		7	3	6	12.07.2004	1	5	1	1	1
209	M	12.01.2002	03.18.2005	2	7	10	3	0	2	2	3	6	1	1	1	8	3	1	03.09.2005	3	1	1	1	2
210	M	09.01.2004	08.31.2005	2	12	13	1	0	0	2	3	6	1	1	1	2	3	1	08.25.2005	3	5	1	1	2
211	F	04.11.2005	11.09.2005	1	7	7	5	1	1	1	3	5	1	3		9	3	6	10.28.2005	2	2	1	1	1
212	F	06.01.2003	12.02.2005	2	3	6	3	0	0	2	3	6	1	1	2	7	3	2	11.22.2005	2	5	1	1	2
213	F	08.01.2003	08.30.2006	2	10	12	3	0	2	1	3	3	1	1	1	7	1	6	02.03.2006	2	1	1	1	1
214	M	05.23.2006	12.12.2006	1	8	8	3	1	2	2	3	6	1	1	1	2	3	6	08.22.2006	3	1	2	1	2
215	F	01.01.1997	07.26.2006	2	3	12	1	0	2	2	3	6	1	2	1	2	3	4	07.22.2006	1	1	1	1	1
216	M	03.01.2006	10.11.2006	1	10	10	1	1	1	2	3	6	1	3		7	3	6	08.22.2006	1	1	2	1	1
217	M	03.02.2007	11.20.2007	1	11	12	1	2	1	1	3	6	2	1		4	3	1	10.26.2007	1	1	1	1	1
218	F	08.01.2001	09.26.2007	2	5	10	1	0	2	2	3	6	1	3	1	7	3	6	NA	1	1	1	1	2

219	M	07.22.2004	11.29.2007	2	8	11	3	1	2	2	3	6	1	3		7	3	2	10.27.2007	1	1	1	1	1
220	M	06.01.2005	07.23.2008	2	3	6	3	2	2	2	3	6	1	3	NA	7	3	2	06.27.2008	3	1	1	1	2
221	F	11.01.2006	08.13.2008	2	8	10	1	2	2	2	3	6	2	2	1	9	3	1	08.05.2008	4	1	1	1	2
222	M	11.08.2003	01.28.2008	2	2	7	3	1	2	2	3	6	1	3		7	3	2	01.12.2008	2	5	1	1	1
223	F	01.01.2002	02.13.2008	2	5	11	3	3	2	2	3	6	1	2	1	7	3	4	09.26.2007	3	0	1	1	2
224	F	11.13.2006	05.21.2008	2	8	10	1	1	2	1	3	4	2	1	2	7	1	2	01.01.2008	1	5	1	1	2
225	F	01.01.2004	06.04.2008	2	10	14	1	1	2	2	3	6	1	2	3	9	1	1	04.02.2008	4	2	1	1	2
226	F	07.01.2006	05.13.2008	2	12	14	1	0	2	2	3	6	1	1	1	8	1	1	04.26.2008	2	2	2	1	2
227	M	03.01.2007	02.25.2008	1	10	11	1	2	2	2	3	6	1	1		2	1	1	11.14.2007	1	2	1	1	1
228	M	03.06.2006	07.23.2008	2	4	6	3	2	2	2	3	5	1	3		7	3	3	03.07.2008	2	1	1	1	1
229	M	01.01.2001	03.20.2009	2	5	13	3	2	2	2	3	6	1	3		7	3	2	06.13.2006	1	1	1	1	1
230	M	04.03.2007	06.24.2009	2	6	8	3	1	2	2	3	6	2	1		7	3	1	01.22.2008	2	1	1	1	1
231	M	04.01.2008	06.17.2009	2	5	9	1	1	0	0	3	6	1	1		7	1	6	06.02.2009	1	1	1	1	1
232	M	01.01.1995	12.01.1995	1	14	14	1	0	1	2	3	6	1	3		11	2	1	NA	0	0	1	1	1
233	M	01.01.1992	09.21.1995	2	4	7	3	0	2	2	3	6	1	2	1	1	2	2	02.05.1994	3	2	1	1	1
234	F	02.01.1993	02.20.1996	2	6	9	1	1	0	0	0	6	1	3		9	3	1	NA	1	5	1	1	0
235	M	01.01.1992	12.01.1996	2	6	10	2	0	0	0	3	6	1	3		0	2	2	NA	1	1	1	1	0
236	M	12.01.1995	05.27.1997	2	2	4	1	0	0	0	3	6	1	2	2	1	1	1	05.10.1997	2	0	1	1	1
237	M	10.01.1997	10.15.1998	2	8	9	3	0	0	0	3	6	1	1		1	1	3	NA	1	0	1	1	1
238	M	01.01.1996	01.12.1999	2	3	6	1	2	2	2	3	6	1	3		2	3	6	08.04.1998	1	5	1	1	1
239	F	04.09.1998	06.15.1999	2	10	10	2	1	1	2	3	6	1	3		2	3	1	NA	1	0	1	1	1
240	M	12.25.1996	09.06.1999	2	9	12	3	0	2	2	3	6	1	2	2	8	1	6	05.28.1999	4	2	1	1	2
241	F	10.01.1998	12.13.1999	2	6	7	3	0	0	2	3	6	2	1		7	3	3	08.03.1999	1	0	1	1	0
242	M	07.01.2000	02.28.2001	1	5	6	3	3	0	0	3	6	1	1	1	8	1	5	NA	2	1	1	2	1
243	M	03.01.2000	05.20.2002	2	10	12	3	0	1	2	3	6	2	1		9	3	2	05.09.2002	1	5	1	1	1
244	F	04.19.2002	08.18.2003	2	12	13	3	1	0	0	3	2	1	3	1	7	3	3	07.30.2003	3	1	1	1	1
245	F	12.01.2000	09.15.2004	2	4	8	3	1	2	2	3	6	1	3		9	3	6	01.23.2004	1	5	1	1	1
246	F	01.01.2005	07.11.2005	1	5	6	1	2	2	2	3	6	1	3		7	3	1	07.01.2005	2	2	1	1	1
247	M	10.01.2002	03.17.2006	2	5	9	3	1	2	2	3	6	1	3		7	3	3	10.21.2005	1	1	1	1	1
248	F	01.01.2004	05.03.2006	2	7	9	3	2	0	2	3	6	1	1	2	7	1	5	05.02.2006	3	1	1	2	2
249	M	05.01.2003	10.23.2007	2	9	13	3	2	0	0	3	6	1	2	1	7	1	6	09.07.2007	4	1	2	1	2
250	F	07.01.2006	11.28.2007	2	4	5	1	3	1	2	3	6	1	3		9	3	3	11.19.2007	1	1	1	1	1
251	M	11.01.2005	11.28.2007	2	10	12	1	1	2	0	33	6	1	2	2	7	1	6	11.09.2007	2	1	1	1	2
252	M	01.01.2003	08.22.2008	2	10	14	3	1	2	2	3	6	2	2	1	1	2	3	NA	0	1	1	1	2
253	F	03.27.2006	03.05.2008	2	12	14	4	1	1	2	3	6	1	1	1	7	1	4	02.27.2008	2	1	1	1	2
254	M	01.01.2006	04.23.2008	2	10	12	3	2	2	1	3	6	1	3		7	3	1	11.01.2007	1	5	1	1	1

Spln	SHPR	PerSCo	AB	HS	IPoSR	DOIPoSR	PePC	TtPePC	IPoSRDr	PoSLOR	DOPoSLOR	PoSR-2mo	TPoSLOR	OAT&R-Ref	DOLFU	PLFU	TLFU	D/A	Res/Ref	FR-LFU	OFUS	Res-DOR	Ref-DOR	DODe
2	3	5	1	12	2	03.17.1995	751000	10	1	0	NA	2	7	NA	03.24.1995	751000	1	1	1	6	2	03.15.1997	NA	NA
0	0	5	2	NA	2	05.24.1995	522000	7	1	0	NA	2	7	NA	05.30.1995	522000	1	1	1	6	2	05.24.1995	NA	NA
0	0	5	2	NA	2	06.23.1995	306200	10	1	0	NA	2	7	NA	06.30.1995	306200	1	1	1	6	2	06.23.1995	NA	NA
0	0	5	2	NA	1	08.12.1995	88000	1	1	0	NA	1	7	NA	02.26.2002	172000	1	1	1	6	2	11.09.1995	NA	NA
0	0	5	2	NA	2	11.16.1995	146600	10	1	0	NA	2	7	NA	11.23.1995	146600	1	1	1	6	2	11.16.1995	NA	NA
2	1	5	2	7	2	03.10.1996	325000	7	1	2	NA	2	6	NA	07.15.2009	130000	1	1	1	6	1	03.10.1996	NA	NA
0	0	5	2	NA	2	03.29.1996	884000	10	1	0	NA	2	7	NA	04.05.1996	884000	1	1	1	6	2	03.29.1996	NA	NA
0	0	5	2		2	07.19.1996	285000	3	1	0	NA	2	7	NA	06.14.2005	247000	1	1	1	6	2	07.17.1996	NA	NA
0	0	0	0	NA	2	12.02.1996	160000	30	1	2	NA	2	6	NA	03.20.2009	168000	1	1	1	6	1	12.02.1996	NA	NA
0	0	5	2	NA	2	11.02.1996	574000	7	1	0	NA	2	7	NA	11.08.1996	574000	1	1	1	6	2	11.02.1996	NA	NA
2	1	5	2	12	2	12.06.1996	355000	10	1	0	NA	2	7	NA	12.13.1996	355000	1	1	1	6	2	12.04.1996	NA	NA
2	0	5	2	12	2	12.03.1996	203000	3	1	0	NA	2	7	NA	12.09.1996	136000	1	1	1	6	2	12.03.1996	NA	NA
2	1	5	1	19	2	03.15.1996	335000	7	1	2	NA	2	6	NA	08.31.2009	134000	1	1	1	6	1	03.13.1996	NA	NA
2	1	5	2	24	2	02.17.1997	148000	3	1	0	NA	2	7	NA	02.23.1997	147000	1	1	1	6	2	02.15.1997	NA	NA
2	2	5	1	7	1	05.27.1997	132000	1	1	0	NA	1	7	NA	06.02.1997	60000	1	1	1	6	2	05.27.1997	NA	NA
2	1	5	1	14	1	09.12.1997	67000	1	1	0	NA	1	7	NA	09.18.1997	48000	2	1	1	6	2	09.12.1997	NA	NA
2	3	5	1	6	2	01.31.1998	287000	10	1	0	NA	2	7	NA	02.08.1998	287000	1	1	1	6	2	01.29.1998	NA	NA
0	0	5	2	18	2	03.05.1998	637000	7	1	0	NA	2	7	NA	03.14.1998	637000	1	1	1	6	2	03.05.1998	NA	NA
2	1	5	1	30	2	04.01.1998	407000	14	1	0	NA	2	7	NA	04.13.1998	407000	1	1	1	6	2	04.01.1998	NA	NA
0	0	5	0	10	2	05.21.1998	457000	50	1	0	NA	2	7	NA	04.02.2003	597000	1	1	1	6	2	05.21.1998	NA	NA
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2	1	5	2	4	1	06.25.2009	119000	7	1	0	NA	1	7	NA	06.30.2009	119000	1	1	1	6	2	06.25.2009	NA	NA
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